"Primary Abstract","Primary Paper","Secondary Abstract","Secondary Paper","Duplicate","Have PDF","Year","Author","Title","Journal","Issue","Id","DuplicateOf","Abstract","Primary Comment","Secondary Comment","Source","pmid","pub_date","pub_affiliation","pub_authorlang","pub_journal","pub_journalshort","pub_place","pub_type","pub_issn"
"Unknown","Unknown","Unknown","Unknown","","","2014","O'Flaherty, C.","Iatrogenic genetic damage of spermatozoa","Adv. Exp. Med. Biol.","791:117-135","2ef256b5-5f2d-475a-b7b2-72aeecd35c31","","Various factors that negatively influence male fertility can affect sperm morphology and physiology. Many studies on humans and animals suggest that both radiation and chemotherapy alter the sperm chromatin, inducing significant damage to sperm DNA, and decrease the level of protamination, thereby altering DNA compaction. Spermatozoa from cancer survivors are affected by chemotherapy even years after the end of treatment. We are exposed to various toxicants present in the environment (e.g., products of air pollution, pesticides, and plasticizers) whose impact on human male reproduction has not yet been established. This chapter aims to update our knowledge on how the sperm chromatin structure is modified by external agents and to describe the different strategies available to better study this complex structure in infertile men. Â© 2014 Springer Science+Business Media New York.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Chambas, I., Coudert, P.","Ferret, a new companion animal (2/2): Care, pathologies, treatments","","(485):20-22","1265ddc9-58c3-4a28-a1cf-3da1bfd879d5","","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2004","Alavanja, M. C., Dosemeci, M., Samanic, C., Lubin, J., Lynch, C. F., Knott, C., Barker, J., Hoppin, J. A., Sandler, D. P., Coble, J., Thomas, K., Blair, A.","Pesticides and lung cancer risk in the agricultural health study cohort","American journal of epidemiology","160(9):876-85","78dda231-9ab5-4077-92b8-7270f911ac07","","The authors examined the relation between 50 widely used agricultural pesticides and lung cancer incidence in the Agricultural Health Study, a prospective cohort study of 57,284 pesticide applicators and 32,333 spouses of farmer applicators with no prior history of lung cancer. Self-administered questionnaires were completed at enrollment (1993-1997). Cancer incidence was determined through population-based cancer registries from enrollment through December 31, 2001. A lung cancer standardized incidence ratio of 0.44 (95% confidence interval: 0.39, 0.49) was observed overall, due in large part to a low cigarette smoking prevalence. Two widely used herbicides, metolachlor and pendimethalin (for low-exposed groups to four higher exposure categories: odds ratio (OR) = 1.0, 1.6, 1.2, 5.0; p(trend) = 0.0002; and OR = 1.0, 1.6, 2.1, 4.4; p(trend) = 0.003, respectively), and two widely used insecticides, chlorpyrifos and diazinon (OR = 1.0, 1.1, 1.7, 1.9; p(trend) = 0.03; and OR = 1.0, 1.6, 2.7, 3.7; p(trend) = 0.04, respectively), showed some evidence of exposure response for lung cancer. These excesses could not be explained by previously identified lung cancer risk factors. The usage levels in this cohort are considerably higher than those typically experienced by the general population. An excess risk among spouses directly exposed to pesticides could not be evaluated at this time.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Beane Freeman, L. E., Bonner, M. R., Blair, A., Hoppin, J. A., Sandler, D. P., Lubin, J. H., Dosemeci, M., Lynch, C. F.,

Knott, C., Alavanja, M. C.","Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon","American journal of epidemiology","162(11):1070-9","5b7d8718-3793-4d1d-99e4-956dabb7eabd","","Little is known about the potential carcinogenicity associated with routine application of diazinon, a common organophosphate insecticide. The authors explored a possible association of diazinon exposure with cancer risk in the Agricultural Health Study, a prospective cohort of licensed pesticide applicators in Iowa and North Carolina enrolled in 1993-1997. A total of 23,106 male applicators provided information in a self-administered questionnaire. Among 4,961 applicators who reported using diazinon, 301 incident cancer cases were diagnosed during the follow-up period ending December 2002 compared with 968 cases among 18,145 participants who reported no use. Poisson regression was used to calculate rate ratios and 95% confidence intervals. Two quantitative exposure metrics were used: lifetime exposure days and intensity-weighted lifetime exposure days, a measure that incorporates probability of pesticide exposure with lifetime pesticide application frequency. When lifetime exposure days were used, increased risks for the highest tertile of exposure and significant tests for trend for lung cancer and leukemia were observed. No other cancer site showed an association with diazinon for the highest tertile of exposure. Because these results were based on small numbers, additional analyses are necessary as more cases accrue to clarify whether diazinon is associated with cancer risk in humans.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","1998","Blair, A., Cantor, K. P., Zahm, S. H.","Non-hodgkin's lymphoma and agricultural use of the insecticide lindane","American journal of industrial medicine","33(1):82-7","e994c9bb-67f8-4926-a1b5-52a8a4f8d204","","Data from population-based case-control studies of non-Hodgkin's lymphoma among white men from Kansas, Nebraska, Iowa, and Minnesota were pooled to evaluate potential risks from environmental exposures in more detail, while controlling for potential confounding factors. These data provided the opportunity to evaluate the risk of non-Hodgkin's lymphoma from potential exposures to lindane, a pesticide that causes cancer in laboratory animals and has been associated with human cancer in a few epidemiologic investigations. This pooled data set includes 987 individuals with non-Hodgkin's lymphoma and 2,895 population-based controls. Information was obtained by telephone or in person interviews, which included detailed questions on farm practices and agricultural use of chemicals. Logistic regression was used to calculate odds ratios (ORs) adjusted for age, state of residence, and subject or proxy interviews. Reported use of lindane significantly increased the risk of non-Hodgkin's's lymphoma by 50%. Some use characteristics were suggestive of an association. ORs were greater among persons who first used the pesticide 20 years before diagnosis (OR = 1.7) than more recently (OR = 1.3), among those who reported more frequent use (OR = 2.0 for use 5 or more days per year versus 1.6 for fewer than five days per year), and from use on crops (OR = 1.9), rather than from use on animals (OR = 1.3), although these differences were not statistically significant. On the other hand, ORs were lower when based on direct interviews (OR = 1.3) than on data from proxy respondents (OR = 2.1) and adjustment for potential confounding by use of 2,4-D and diazinon reduced the ORs associated with lindane use from 1.5 to 1.2 and 1.3, respectively. Lindane does not appear to be a major etiologic factor in the development of non-Hodgkin's's lymphoma, although a small role cannot be ruled out.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2013","Koutros, S., Beane Freeman, L.

E., Lubin, J. H., Heltshe, S. L., Andreotti, G., Barry, K. H., Dellavalle, C. T., Hoppin, J. A., Sandler, D. P., Lynch, C. F., Blair, A., Alavanja, M. C. R.","Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study","","177(1):59-74","f44f18e6-23ae-425d-bf2b-44d1a5c7f49e","","Because pesticides may operate through different mechanisms, the authors studied the risk of prostate cancer associated with specific pesticides in the Agricultural Health Study (1993-2007). With 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators, this is the largest study to date. Rate ratios and 95% confidence intervals were calculated by using Poisson regression to evaluate lifetime use of 48 pesticides and prostate cancer incidence. Three organophosphate insecticides were significantly associated with aggressive prostate cancer: fonofos (rate ratio (RR) for the highest quartile of exposure (Q4) vs. nonexposed = 1.63, 95% confidence interval (CI): 1.22, 2.17; Ptrend < 0.001); malathion (RR for Q4 vs. nonexposed = 1.43, 95% CI: 1.08, 1.88; Ptrend = 0.04); and terbufos (RR for Q4 vs. nonexposed = 1.29, 95% CI: 1.02, 1.64; Ptrend = 0.03). The organochlorine insecticide aldrin was also associated with increased risk of aggressive prostate cancer (RR for Q4 vs. nonexposed = 1.49, 95% CI: 1.03, 2.18; Ptrend = 0.02). This analysis has overcome several limitations of previous studies with the inclusion of a large number of cases with relevant exposure and detailed information on use of specific pesticides at 2 points in time. Furthermore, this is the first time specific pesticides are implicated as risk factors for aggressive prostate cancer. Â© The Author 2012. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2011","Myers, S. L., Hoppin, J. A., Sandler, D. P., Baird, D. D.","Organophosphate pesticide use and selfreported incident uterine fibroids in the agricultural health study","","173:S12","0aa30ce2-0033-4b0f-85b5-5a581359300a","","Uterine fibroids, hormonally-mediated benign tumors, are the leading indication for hysterectomy in the US. Results from a cross-sectional analysis of women enrolled in the Agricultural Health Study suggested an association between organophosphate insecticide use and fibroids. To clarify the temporal relationship between pesticide use and fibroid diagnosis, we conducted a prospective analysis of incident fibroid diagnosis among white women who were less than 55 years old, premenopausal, with intact uteri, and without a previous fibroid diagnosis at baseline (778 incident cases and 10,972 non-cases). Logistic regression was used to estimate the association between pesticide use reported at baseline and self-reported fibroids diagnosed between baseline and 5-year follow-up, controlling for age and state (Iowa/North Carolina). While the cross-sectional analysis had shown a significant increase in fibroids among organophosphate users compared to never users (Odds Ratio [OR]: 1.33; 95% Confidence Interval [CI]: 1.19, 1.48), the association was attenuated in the prospective analysis (OR: 1.19; 95% CI: 0.99, 1.42). When examined individually, the OR for diazinon use was elevated (OR: 1.25, 95% CI: 0.98, 1.58), though slightly less than in the cross-sectional analysis (OR: 1.35; 95% CI: 1.17, 1.55). Users of coumaphos and parathion also had increased odds of fibroids, with ORs of about 1.3, but estimates were imprecise due to small numbers. Although the smaller sample size led to a loss of power, the general pattern of results was consistent with the cross-sectional analysis. Toxicological testing would help determine if and how organophosphates may be related to fibroid development.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2004","Borba da Cunha, A. C., Lopez de

Alda, M. J., Barcelo, D., Pizzolato, T. M., dos Santos, J. H.","Multianalyte determination of different classes of pesticides (acidic, triazines, phenyl ureas, anilines, organophosphates, molinate and propanil) by liquid chromatography-electrospray-tandem mass spectrometry","Analytical and bioanalytical chemistry","378(4):940-54","505bf00a-d5ac-4bc0-b685-dbbb98b555d5","","This work describes the optimization of a liquid chromatography-electrospray-tandem mass spectrometry (LC-ESI-MS-MS) method for the multianalyte determination of twenty pesticides, selected based on current regulations and extent of use. Chromatographic separation was carried out on a Purospher STAR RP-18e column using gradient acetonitrile-water as mobile phase. Triazines, phenylureas, organophosphates, anilines, and molinate were determined in the positive ionization mode, and acidic pesticides and propanil in the negative ion mode. Two different precursor ion-product ion transitions were selected for each analyte and monitored under time scheduled multiple reaction monitoring (MRM) conditions. The optimized method was shown to be linear in the range 1 to 1000 ng/mL with correlation coefficients higher than 0.99 for all but one (diazinon) of the analytes, very sensitive (with limits of detection between 0.010 and 4.528 ng/mL), and repeatable (with relative standard deviations, calculated from the replicate analysis of standard mixtures, lower than 14%). The present work was also devoted to the elucidation of the structures of the principal fragment ions obtained after collision-induced dissociation of the pesticides investigated, an aspect often overlooked in the literature.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2010","Andersen, H. B., Caldwell, R. S., Toll, J., Do, T., Saban, L.","Sensitivity of lamprey ammocoetes to six chemicals","Archives of environmental contamination and toxicology","59(4):622-31","7c67f846-0f99-4d0b-9f6b-2fa679a97683","","As part of the ecological risk assessment for Portland Harbor Superfund site, a study was conducted to address the question of whether the use of surrogate species in the risk assessment would be protective of lamprey ammocoetes. The study evaluated the acute toxicity of six chemicals: pentachlorophenol, copper, diazinon, aniline, naphthalene, and lindane; these chemicals represent the toxic modes of action of oxidative phosphorylation uncoupler, gill dysfunction, acetylcholinesterase inhibitor, polar narcosis, narcosis, and central nervous system interference, respectively. Field-collected lamprey ammocoetes were exposed to each of the six chemicals in a definitive 96-h flow-through acute water-only toxicity test. LC(50)s were calculated for pentachlorophenol at 31 mug/l, copper at 46 mug/l, diazinon at 8.9 mg/l, and aniline at 430 mg/l. Species sensitivity distributions based on LC(50)s for aquatic organisms indicated that lamprey ammocoetes were relatively sensitive to pentachlorophenol (15th percentile). The sensitivity of lamprey ammocoetes to copper approximated the average of aquatic species tested (46th percentile). Lamprey ammocoetes were relatively insensitive to diazinon and aniline (72nd and 90th percentile, respectively). The 96-h LC(50) for naphthalene was estimated at 10 mg/l, based on 50% mortality in the highest concentration. Based on a comparison with LC(50)s for four other fish species, ranging from 2.0 to 6.6 mg/l, lamprey ammocoetes were relatively insensitive to naphthalene. A 96-h LC(50) could not be derived for lindane, with 12.5% mortality in the highest test concentration of 2.68 mg/l. LC(50)s for numerous other fish species ranged from 0.001 to 0.24 mg/l, indicating that lamprey ammocoetes were relatively insensitive to lindane. The study concluded that the use of surrogate species in the ecological risk assessment for Portland Harbor would be protective of lamprey

ammocoetes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Sidiropoulou, E., Sachana, M., Flaskos, J., Harris, W., Hargreaves, A. J., Woldehiwet, Z.","Diazinon oxon affects the differentiation of mouse N2a neuroblastoma cells","Archives of toxicology","83(4):373-80","e90f0c58-6d9b-4a4a-a6ca-976b0e65de10","","The aim of this study was to assess the neurotoxicity of diazinon oxon (DZO), a major in vivo metabolite of the phosphorothionate insecticide diazinon (DZ), on differentiating mouse N2a neuroblastoma cells. When used at concentrations of 1, 5 and 10 microM, DZO did not cause cell death but it impaired the outgrowth of axon-like processes after 24 h. Densitometric scanning of Western blots of lysates of N2a cells revealed that exposure to 5 or 10 microM DZO for 24 h increased the expression of phosphorylated neurofilament heavy chain (NFH) compared to controls, while there was no significant change in total NFH. By contrast, treatment of N2a cells with 1-10 microM DZO resulted in marked reductions in the expression of the axon growth-associated protein GAP-43. DZO-treated cells also showed an increased expression of the heat shock protein HSP-70 compared to controls. The above biochemical changes were not temporally related to inhibition of acetylcholinesterase (AChE). These data suggest that biologically relevant, subcytotoxic levels of DZO may exert neurotoxic effects on differentiating cells and that the mechanisms involved are different from those attributed to its parent compound.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","YusÃ , V., CoscollÃ , C., Millet, M.","New screening approach for risk assessment of pesticides in ambient air","","96:322-330","98de1f56-69e5-40e7-9071-0fa54bb88f7b","","We present a novel screening approach for inhalation risk assessment of currently used pesticides (CUPs) in ambient air, based on the measurements of pesticide levels in the inhalable fraction of the particulate matter (PM10). Total concentrations in ambient air (gas+particle phases) were estimated using a theoretical model of distribution of semi-volatile organic compounds between the gas and the particulate phase based on the octanol-air partition (Koa) of each pesticide. The proposed approach was used in a pilot study conducted in a rural station in Valencia (Spain) from April through to October 2010. Twenty out of 82 analysed pesticides were detected in average concentrations ranging from 1.63 to 117.01pgm-3. For adults, children and infants the estimated chronic inhalation risk, expressed as Hazard Quotient (HQ) was <1 for all pesticides. Likewise, the cumulative exposure for detected organophosphorus, pyrethroids and carbamates pesticides, was estimated using as metrics the Hazard Index (HI), which was less than 1 for the three families of pesticides assessed. The cancer risk estimated for the detected pesticides classified as Likely or Possible carcinogens was less than 1.15E-7 for infants. In our opinion, the screening approach proposed could be used in the monitoring and risk assessment of pesticides in ambient air. Â© 2014 Elsevier Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Sachana, M., Sidiropoulou, E., Flaskos, J., Harris, W., Robinson, A. J., Woldehiwet, Z., Hargreaves, A. J.","Diazoxon disrupts the expression and distribution of betaIII-tubulin and MAP 1B in differentiating N2a cells","Basic & clinical pharmacology & toxicology","114(6):490-6","275e854c-eb7c-4f1a-aa54-5f93a6bae41a","","This study aimed at assessing the effects of diazoxon (DZO), a major metabolite of the insecticide diazinon (DZ), on key cytoskeletal proteins in differentiating N2a neuroblastoma cells. Initial experiments established that sublethal concentrations of 1, 5 and 10 muM DZO produced profound

inhibition of neurite outgrowth. Densitometric scanning of probed immunoblots of N2a cell lysates demonstrated that DZO had no effect on total beta-tubulin levels. However, probing with a monoclonal antibody that recognised specifically the betaIII-tubulin isotype revealed that 10 muM DZO induced a significant reduction in the levels of this particular form. Levels of polyglutamylated tubulin were not altered. Exposure to 10 muM DZO also decreased the expression of microtubule-associated protein 1B (MAP 1B). However, DZO had no effect on the expression of MAP tau. DZO also failed to affect the levels neurofilament light (NFL) and neurofilament medium (NFM) chain levels. Indirect immunofluorescence demonstrated that the staining of neurites in treated cells was weaker than in the controls for betaIII-tubulin. In conclusion, DZO disrupts the microtubule (MT) network affecting the expression and distribution of two specific MT proteins known to be important in neuritogenesis. DZO may contribute to the developmental neurotoxicity seen following exposure to DZ.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Han, Q., Robinson, H., Li, J.","Biochemical identification and crystal structure of kynurenine formamidase from Drosophila melanogaster","","446(2):253-260","b8adc265-736f-443d-9ac9-8cf1ab34df03","","KFase (kynurenine formamidase), also known as arylformamidase and formylkynurenine formamidase, efficiently catalyses the hydrolysis of NFK (N-formyl-L-kynurenine) to kynurenine. KFase is the second enzyme in the kynurenine pathway of tryptophan metabolism. A number of intermediates formed in the kynurenine pathway are biologically active and implicated in an assortment of medical conditions, including cancer, schizophrenia and neurodegenerative diseases. Consequently, enzymes involved in the kynurenine pathway have been considered potential regulatory targets. In the present study, we report, for the first time, the biochemical characterization and crystal structures of Drosophila melanogaster KFase conjugated with an inhibitor, PMSF. The protein architecture of KFase reveals that it belongs to the Î±/Î± hydrolase fold family. The PMSF-binding information of the solved conjugated crystal structure was used to obtain a KFase and NFK complex using molecular docking. The complex is useful for understanding the catalytic mechanism of KFase. The present study provides a molecular basis for future efforts in maintaining or regulating kynurenine metabolism through the molecular and biochemical regulation of KFase. Â© The Authors Journal compilation Â© 2012 Biochemical Society.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2002","Pabarcus, M. K., Casida, J. E.","Kynurenine formamidase: determination of primary structure and modeling-based prediction of tertiary structure and catalytic triad","Biochimica et biophysica acta","1596(2):201-11","792b1b46-a794-4a83-8279-8f253b147018","","Kynurenine formamidase (KFase) (EC 3.5.1.9) hydrolyzes N-formyl-L-kynurenine, an obligatory step in the conversion of tryptophan to nicotinic acid. Low KFase activity in chicken embryos, from inhibition by organophosphorus insecticides and their metabolites such as diazoxon, leads to marked developmental abnormalities. While KFase was purportedly isolated previously, the structure and residues important for catalysis and inhibition were not established. KFase was isolated here from mouse liver cytosol by (NH4)2SO4 precipitation and three FPLC steps (resulting in 221-fold increase in specific activity for N-formyl-L-kynurenine hydrolysis) followed by conversion to [3H]diethylphosphoryl-KFase and finally isolation by C4 reverse-phase high-performance liquid chromatography. Determination of tryptic fragment amino acid sequences and cDNA cloning produced a new 305-amino-acid protein sequence. Although an amidase by function, the primary structure

of KFase lacks the amidase signature sequence and is more similar to esterases and lipases. Sequence profile analysis indicates KFase is related to the esterase/lipase/thioesterase family containing the conserved active-site serine sequence GXSXG. The alpha/beta-hydrolase fold is suggested for KFase by its primary sequence and predicted secondary conformation. A three-dimensional model based on the structures of homologous carboxylesterase EST2 and brefeldin A esterase implicates Ser162, Asp247 and His279 as the active site triad.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2011","Yamamoto, K., Ichinose, H., Aso, Y., Banno, Y., Kimura, M., Nakashima, T.","Molecular characterization of an insecticide-induced novel glutathione transferase in silkworm","Biochimica et biophysica acta","1810(4):420-6","da6bef02-df42-471b-a59a-9cd109e43b82","","BACKGROUND: The glutathione transferase (GST) superfamily is involved in the detoxification of various xenobiotics. We have identified a GST mRNA that was induced in the fat bodies of a silkworm strain exhibiting diazinon resistance and have investigated the enzyme properties of this GST. METHODS: A soluble recombinant protein was overexpressed in Escherichia coli. Amino acid residues of interest were changed to alanine by site-directed mutagenesis. RESULTS AND CONCLUSIONS: Phylogenetic analysis of the deduced amino acid sequence indicates that this GST belongs to an unclassified group previously reported in mosquitoes. This enzyme, named bmGSTu, has highly conserved amino acid residues, including Tyr7, Ser12 and Asn50. A recombinant bmGSTu was able to catalyze the biotranslation of glutathione with 1-chloro-2,4-dinitrobenzene, a synthetic substrate of GST. Kinetic analysis of bmGSTu mutants indicated that Tyr7, Ser12 and Asn50 are involved in enzyme function. GENERAL SIGNIFICANCE: These results support the hypothesis that bmGSTu may play a role in insecticide resistance in Bombyx mori.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2011","McCollum, C. W., Ducharme, N. A., Bondesson, M., Gustafsson, J. A.","Developmental toxicity screening in zebrafish","","93(2):67-114","615e5870-dde3-4cbc-986a-4e49afcafd2d","","Given the ever-increasing toxic exposure ubiquitously present in our environment as well as emerging evidence that these exposures are hazardous to human health, the current rodent-based regulations are proving inadequate. In the process of overhauling risk assessment methodology, a nonrodent test organism, the zebrafish, is emerging as tractable for medium- and high-throughput assessments, which may help to accelerate the restructuring of standards. Zebrafish have high developmental similarity to mammals in most aspects of embryo development, including early embryonic processes, and on cardiovascular, somite, muscular, skeletal, and neuronal systems. Here, we briefly describe the development of these systems and then chronicle the toxic impacts assessed following chemical exposure. We also compare the available data in zebrafish toxicity assays with two databases containing mammalian toxicity data. Finally, we identify gaps in our collective knowledge that are ripe for future studies. Â© 2011 Wiley-Liss, Inc.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2010","Adigun, A. A., Ryde, I. T., Seidler, F. J., Slotkin, T. A.","Organophosphate exposure during a critical developmental stage reprograms adenylyl cyclase signaling in PC12 cells","Brain research","1329:36-44","d1795079-9e62-4ba9-8821-47380218207d","","Early-life organophosphate (OP) exposures elicit neurobehavioral deficits through mechanisms other than inhibiting cholinesterase. Cell signaling cascades are postulated as critical

noncholinesterase targets that mediate both the initial alterations in neurodevelopment as well as subsequent abnormalities of synaptic function. We exposed PC12 cells to chlorpyrifos, diazinon or parathion in the undifferentiated state and during neurodifferentiation; we then assessed the function of the adenylyl cyclase (AC) signaling cascade, measuring basal AC activity as well as responses to stimulants acting at G-proteins or on the AC molecule itself. In undifferentiated cells, a 2day exposure to the OPs had no significant effect on AC signaling but the same treatment in differentiating cells produced deficits in all AC measures when exposure commenced at the initiation of differentiation. However, when exposure of the differentiating cells was continued for 6days, AC activities then became supranormal. The same increase was obtained if cells were exposed only for the first two days of differentiation, followed by four subsequent days without the OPs. Furthermore, the OP effects on cell signaling were entirely distinct from those on indices of cell number and neurite outgrowth. These results indicate that OP exposure reprograms the AC pathway during a discrete developmental stage at the commencement of neurodifferentiation, with effects that continue to emerge after OP exposure is discontinued. Importantly, the same sequence is seen with OP exposures in neonatal rats, indicating that direct effects of these agents to reprogram cell signaling provide a major mechanism for functional effects unrelated to cholinesterase inhibition.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Adigun, A. A., Seidler, F. J., Slotkin, T. A.","Disparate developmental neurotoxicants converge on the cyclic AMP signaling cascade, revealed by transcriptional profiles in vitro and in vivo","Brain research","1316:1-16","9e0688ab-4377-4744-9d82-432d4bcdfd5e","","Cell-signaling cascades are convergent targets for developmental neurotoxicity of otherwise unrelated agents. We compared organophosphates (chlorpyrifos, diazinon), an organochlorine (dieldrin) and a metal (Ni(2+)) for their effects on neuronotypic PC12 cells, assessing gene transcription involved in the cyclic AMP pathway. Each agent was introduced during neurodifferentiation at a concentration of 30 microM for 24 or 72 h and we assessed 69 genes encoding adenylyl cyclase isoforms and regulators, G-protein alpha-and beta,gamma-subunits, protein kinase A subtypes and the phosphodiesterase family. We found strong concordance among the four agents across all the gene families, with the strongest relationships for the G-proteins, followed by adenylyl cyclase, and lesser concordance for protein kinase A and phosphodiesterase. Superimposed on this pattern, chlorpyrifos and diazinon were surprisingly the least alike, whereas there was strong concordance of dieldrin and Ni(2+) with each other and with each individual organophosphate. Further, the effects of chlorpyrifos differed substantially depending on whether cells were undifferentiated or differentiating. To resolve the disparities between chlorpyrifos and diazinon, we performed analyses in rat brain regions after in vivo neonatal exposures; unlike the in vitro results, there was strong concordance. Our results show that unrelated developmental neurotoxicants can nevertheless produce similar outcomes by targeting cell signaling pathways involved in neurodifferentiation during a critical developmental period of vulnerability. Nevertheless, a full evaluation of concordance between different toxicants requires evaluations of in vitro systems that detect direct effects, as well as in vivo systems that allow for more complex interactions that converge on the same
pathway.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Slotkin, T. A., Seidler, F. J.","Protein kinase C is a target for diverse developmental neurotoxicants:

transcriptional responses to chlorpyrifos, diazinon, dieldrin and divalent nickel in PC12 cells","Brain research","1263:23-32","54bc48aa-bb66-4599-937c-2c75502485f2","","Unrelated developmental neurotoxicants can elicit similar functional outcomes, whereas agents in the same class may differ. We compared two organophosphate insecticides (chlorpyrifos, diazinon) with an organochlorine (dieldrin) and a metal (Ni(2+)) for similarities and differences in their effects on gene expression encoding subtypes of protein kinase C and their modulators, a cell signaling cascade that integrates the actions of neurotrophic factors involved in brain development. We conducted evaluations in PC12 cells, a model for neuronal development, with each agent introduced at 30 microM for 24 or 72 h, treatments devoid of cytotoxicity. Chlorpyrifos evoked by far the largest effect, with widespread upregulation of multiple genes; the effects were greater during neurodifferentiation than when cells were exposed prior to differentiation. Diazinon had smaller and less widespread effects, consistent with its lesser long-term impact on synaptic function and behavior noted for in vivo exposures in developing rats. Surprisingly, the effects of diazinon, dieldrin and Ni(2+) showed basic similarities despite the fact that all three come from different classes of toxicants. Our findings provide some of the first evidence for a specific mechanistic cascade contributing to the cholinesterase-independent developmental neurotoxicant actions of chlorpyrifos and its differences from diazinon, while at the same time identifying mechanistic convergence between otherwise unrelated toxicants that provides predictions about common neurodevelopmental outcomes. These results further show how combined use of cell cultures and microarray technology can guide future in vivo work on diverse developmental neurotoxicants.","","","RefMan","","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2010","Slotkin, T. A., Seidler, F. J.","Diverse neurotoxicants converge on gene expression for neuropeptides and their receptors in an in vitro model of neurodifferentiation: effects of chlorpyrifos, diazinon, dieldrin and divalent nickel in PC12 cells","Brain research","1353:36-52","4cbe87b9-e344-403b-87d5-fb8b7a06287e","","Unrelated developmental neurotoxicants can produce similar neurobehavioral outcomes. We examined whether disparate agents affect neuromodulators that control numerous neurotransmitters and circuits, employing PC12 cells to explore the targeting of neuroactive peptides by organophosphates (chlorpyrifos, diazinon), an organochlorine (dieldrin) and a metal (Ni(2+)); we utilized microarrays to profile gene expression for the peptides and their receptors. Chlorpyrifos evoked robust upregulation of cholecystokinin, corticotropin releasing hormone, galanin, neuropeptide Y, neurotensin, preproenkephalin and tachykinin 1; this involved a critical period at the commencement of neurodifferentiation, since the effects were much less notable in undifferentiated PC12 cells. Diazinon targeted a similar but smaller repertoire of neuropeptide genes and the magnitude of the effects was also generally less. Surprisingly, dieldrin shared many of the same neuropeptide targets as the organophosphates and concordance analysis showed significant overlap among all three pesticides. However, dieldrin had more notable effects on neuropeptide receptors, and overlap between diazinon and dieldrin for the receptors led to a stronger resemblance of these two agents than of chlorpyrifos and dieldrin. Ni(2+) was unique, evoking upregulation of only one of the peptides affected by the other agents, while causing downregulation of several others. Nevertheless, there was still significant concordance between Ni(2+) and either diazinon or dieldrin, reflecting similarities toward the receptors. Our results show that neuropeptides are likely to be a prominent target for the developmental neurotoxicity of organophosphates and other

neurotoxicants, and further, that the convergence of disparate agents on the same genes and pathways may contribute to similar neurobehavioral outcomes.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2009","Slotkin, T., Seidler, F.","Transcriptional profiles reveal similarities and differences in the effects of developmental neurotoxicants on differentiation into neurotransmitter phenotypes in PC12 cells","Brain research bulletin","78(4-5):211-25","8ed06be9-958b-4e72-ad3a-b4cf262227a7","","Unrelated developmental neurotoxicants nevertheless converge on common functional and behavioral outcomes. We used PC12 cells, a model of neuronal development, to explore similarities and differences for organophosphate pesticides (chlorpyrifos, diazinon), an organochlorine pesticide (dieldrin) and a metal (Ni(2+)), focusing on transcriptional profiles related to differentiation into acetylcholine, dopamine and norepinephrine phenotypes. Agents were introduced at 30 microM for 24 or 72 h, treatments devoid of cytotoxicity. Using microarrays, we examined the mRNAs encoding the proteins involved in neurotransmitter biosynthesis, storage, and degradation, along with the complete panoply of receptors for each transmitter. All three pesticides evoked concordant patterns of effects on genes involved in neural growth and neurite extension, with a distinctly different pattern for Ni(2+). All four toxicants promoted differentiation into the dopamine phenotype at the expense of the acetylcholine phenotype, involving separable effects of each agent on the various gene families; however, there were major differences in the ability of each to promote or repress the norepinephrine phenotype. Chlorpyrifos and diazinon, although displaying many similarities in their transcriptional profiles, also showed major disparities in keeping with their known differences in synaptic and behavioral outcomes after neonatal exposures to these agents in vivo. Surprisingly, there were closer similarities among diazinon, dieldrin and Ni(2+) than for each agent to chlorpyrifos. Our results illustrate how cell culture systems, combined with microarray technology, can screen for developmental neurotoxicants, serving as a model for alternative approaches to the detection and characterization of the impact of exogenous chemicals on brain development.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2010","Slotkin, T. A., Lobner, D., Seidler, F. J.","Transcriptional profiles for glutamate transporters reveal differences between organophosphates but similarities with unrelated neurotoxicants","Brain research bulletin","83(1-2):76-83","6a524f5d-7cc4-4a0e-b9c8-94373d8d825f","","The developmental neurotoxicity of organophosphates involves mechanisms other than their shared property as cholinesterase inhibitors, among which are excitotoxicity and oxidative stress. We used PC12 cells as a neurodevelopmental model to compare the effects of chlorpyrifos and diazinon on the expression of genes encoding glutamate transporters. Chlorpyrifos had a greater effect in cells undergoing nerve growth factor-induced neurodifferentiation as compared to undifferentiated PC12 cells, with peak sensitivity at the initiation of differentiation, reflecting a global upregulation of all the glutamate transporter genes expressed in this cell line. In differentiating cells, chlorpyrifos had a significantly greater effect than did diazinon and concordance analysis indicated no resemblance in their expression patterns. At the same time, the smaller effects of diazinon were highly concordant with those of an organochlorine pesticide (dieldrin) and a metal (divalent nickel). We also performed similar evaluations for the cystine/glutamate exchanger, which provides protection against oxidative stress by moving cystine into the cell; again, chlorpyrifos had the

greatest effect, in this case reducing expression in undifferentiated and differentiating cells. Our results point to excitotoxicity and oxidative stress as major contributors to the noncholinesterase mechanisms that distinguish the neurodevelopmental outcomes between different organophosphates while providing a means whereby apparently unrelated neurotoxicants may produce similar outcomes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Slotkin, T. A., Seidler, F. J.","Developmental exposure to organophosphates triggers transcriptional changes in genes associated with Parkinson's disease in vitro and in vivo","Brain research bulletin","86(5-6):340-7","8c893f4f-75f2-422a-b5f5-774adfaad090","","Epidemiologic studies support a connection between organophosphate pesticide exposures and subsequent risk of Parkinson's disease (PD). We used differentiating, neuronotypic PC12 cells to compare organophosphates (chlorpyrifos, diazinon), an organochlorine (dieldrin) and a metal (Ni(2+)) for their effects on the transcription of PD-related genes. Both of the organophosphates elicited significant changes in gene expression but with differing patterns: chlorpyrifos evoked both up- and downregulation whereas diazinon elicited overall reductions in expression. Dieldrin was without effect but Ni(2+) produced a pattern resembling that of diazinon. We then exposed neonatal rats to chlorpyrifos or diazinon for the first 4 days after birth and examined the expression of PD-related genes in the brainstem and forebrain. Chlorpyrifos had no significant effect whereas diazinon produced significant increases and decreases in expression of the same PD genes that were targeted in vitro. Our results provide some of the first evidence for a mechanistic relationship between developmental organophosphate exposure and the genes known to confer PD risk in humans; but they also point to disparities between different organophosphates that reinforce the concept that their neurotoxic actions do not rest solely on their shared property as cholinesterase inhibitors. The parallel effects of diazinon and Ni(2+) also show how otherwise unrelated developmental neurotoxicants can nevertheless produce similar outcomes by converging on common molecular pathways, further suggesting a need to examine metals such as Ni(2+) as potential contributors to PD risk.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Slotkin, T. A., Seidler, F. J., Fumagalli, F.","Targeting of neurotrophic factors, their receptors, and signaling pathways in the developmental neurotoxicity of organophosphates in vivo and in vitro","Brain research bulletin","76(4):424-38","e62d7358-269c-4047-8b37-8c59cc9003f5","","Neurotrophic factors control neural cell differentiation and assembly of neural circuits. We previously showed that organophosphate pesticides differentially regulate members of the fibroblast growth factor (fgf) gene family. We administered chlorpyrifos and diazinon to neonatal rats on postnatal days 1-4 at doses devoid of systemic toxicity or growth impairment, and spanning the threshold for barely-detectable cholinesterase inhibition. We evaluated the impact on gene families for different classes of neurotrophic factors. Using microarrays, we examined the regional expression of mRNAs encoding the neurotrophins (ntfs), brain-derived neurotrophic factor (bdnf), nerve growth factor (ngf), the wnt and fzd gene families and the corresponding receptors. Chlorpyrifos and diazinon both had widespread effects on the fgf, ntf, wnt and fzd families but much less on the bdnf and ngf groups. However, the two organophosphates showed disparate effects on a number of key neurotrophic factors. To determine if the actions were mediated directly on differentiating neurons, we tested chlorpyrifos in PC12 cells, an in vitro model of neural cell development.

Effects in PC12 cells mirrored many of those for members of the fgf, ntf and wnt families, as well as the receptors for the ntfs, especially during early differentiation, the stage known to be most susceptible to disruption by organophosphates. Our results suggest that actions on neurotrophic factors provide a mechanism for the developmental neurotoxicity of low doses of organophosphates, and, since effects on expression of the affected genes differed with test agent, may help explain regional disparities in effects and critical periods of vulnerability.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Habibollahi, P., Ghahremani, M. H., Azizi, E., Ostad, S. N.","Multi drug resistance-1 (MDR1) expression in response to chronic diazinon exposure: an in vitro study on Caco-2 cells","Bulletin of environmental contamination and toxicology","86(1):105-9","02c7670c-9881-4500-844e-0aa3f20cf91e","","To evaluate the effect of chronic exposure to diazinon in the gastrointestinal tract, Caco-2 cells were made resistant by growing in low concentrations of diazinon (0.02 muM) that was gradually increased to 20 muM within 4.5 months. Resistant cells showed significant higher growth in the presence of 15, 45 and 135 muM of diazinon (96.08, 81.80 and 65.16% of control) compared to parent cells (79.71, 71.76 and 29.50% of control, respectively; p < 0.05). P-glycoprotein (P-gp) expression increased significantly in resistant cells (P-gp to beta-actin ratio 0.586 for parent and 1.255 for resistant cells, respectively; p < 0.05) without any alteration in MDR-1 mRNA level (p > 0.05).","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Alavanja, M. C. R., Ross, M. K., Bonner, M. R.","Reply to Increased cancer burden among pesticide applicators and others due to pesticide exposure","","63(5):366-367","3c5ac179-f0fe-4162-b263-b33cf7207018","","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2001","Waddell, B. L., Zahm, S. H., Baris, D., Weisenburger, D. D., Holmes, F., Burmeister, L. F., Cantor, K. P., Blair, A.","Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States)","Cancer causes & control : CCC","12(6):509-17","f723b07b-db19-423f-aa3d-3da522c90600","","OBJECTIVE: Data from three population-based case-control studies conducted in Kansas, Nebraska, Iowa, and Minnesota were pooled to evaluate the relationship between the use of organophosphate pesticides and non-Hodgkin's lymphoma (NHL) among white male farmers. METHODS: The data set included 748 cases of non-Hodgkin's lymphoma and 2236 population-based controls. Telephone or in-person interviews were utilized to obtain information on the use of pesticides. Odds ratios (OR) adjusted for age, state of residence, and respondent status, as well as other pesticide use where appropriate, were estimated by logistic regression. RESULTS: Use of organophosphate pesticides was associated with a statistically significant 50% increased risk of NHL, but direct interviews showed a significantly lower risk (OR = 1.2) than proxy interviews (OR = 3.0). Among direct interviews the risk of small lymphocytic lymphoma increased with diazinon use (OR = 2.8), after adjustment for other pesticide exposures. CONCLUSIONS: Although we found associations between the risk of NHL and several groupings and specific organophosphate pesticides, larger risks from proxy respondents complicate interpretation. Associations, however, between reported use of diazinon and NHL, particularly diffuse and small lymphocytic lymphoma, among subjects providing direct interviews are not easily discounted.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Saulsbury, M. D., Heyliger, S.,

Li, F., Parker-Johnson, K. T. A.","Knock-down of base excision repair genes increases susceptibility to organophospate pesticide toxicity","","73(8)","1bd0882f-25da-4577-b9e1-56733e0dc786","","Organophosphates are chemicals that inhibit cholinesterases and are employed widely as pesticides. Concerns are increasing regarding the relative safety of these chemicals to the environment. Recent studies suggest organophosphate exposure is associated with increased expression of fragile sites and DNA damage at concentrations that are not associated with cholinesterase inhibition. Chronic exposure to the organophosphate has been associated with high incidences of prostate cancer in farm workers as well as leukemia and non-Hodgkin lymphoma in adults and children. Moreover, a higher degree of DNA damage has been reported in pesticide applicators that have polymorphisms in the base excision repair genes XRCC1 and OGG1. Our laboratory reports that cells deficient in BER enzymes APE1 and OGG1 exhibit a higher cytotoxicity when exposed, in a dose-dependent manner, to organophosphates Chlorpyrifos, Chlorpyrifos-oxon and Isofenphos. However, it should be noted that other organophosphates such as Diazinon and Dichlorvos had very little effects on cellular viability within the APE1 and OGG1 deficient cells. It should be noted that Chlorpyrifos, Chlorpyrifos-oxon and Isofenphos also produce significant oxidative stress in cells. Our data is consistent with previous studies which report a higher degree of DNA damage has been reported in pesticide applicators that have polymorphisms in the base excision repair genes XRCC1 and OGG1. Moreover, our data further suggests that only certain organophosphates, particularly those that induce oxidative stress, may be responsible for toxicity in APE1 and OGG1 deficient cells.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2011","Zhang, X., Wallace, A., Du, P., Baccarelli, A., Jafari, N., Lin, S., Hou, L.","Genome-wide study of DNA methylation alterations in response to pesticide exposure in in vitro","","71(8)","6e90bd3a-0195-4224-b3d0-d63c850b529a","","Pesticides are widely used in the US and worldwide, and are pervasive in our environment. All pesticides sold in the US have passed the Environmental Protection Agency (EPA) screening procedures for carcinogenicity based on their genotoxicity and mutagenicity. However exposure to pesticides among pesticide applicators and manufacturing workers has repeatedly been shown to increase cancer risk, suggesting that pesticides may cause cancer via alternative mechanisms, such as epigenetic changes. The purpose of the present study is to examine whether exposure to organophosphate pesticides (OPs), a group of the most commonly used pesticides in the US, induces DNA methylation alterations in in-vitro. The K562 progenitor blood cell line was exposed to several OPs (i.e., chlorpyrifos, diazinon, fonofos, malathion, parathion, phorate, and terbufos) at different dosages and time periods. DNA was prepared from samples exposed to ethanol (control) and a range of pesticide concentrations similar to exposure levels experienced by the US licensed pesticide applicators. We conducted genomewide DNA methylation analysis using the Illumina Infinium HumanMethylation27 BeadChip that covers 27,578 individual promoter CpG sites in the entire genome. The relative level of methylation was calculated as the ratio of signal from a methylated probe relative to an unmethylated probe. Bayesian-adjusted t-tests were used to identify differentially methylated sites. A cut-off of False Discovery Rate (FDR)-adjusted p-value (q-value) < 0.05 and fold change > 2 was used to identify candidate CpG sites. We observed significant differences in genomewide DNA methylation patterns in relation to exposure to three pesticides (i.e., fonofos, parathion, and terbufos) that have been associated with cancers in human studies. Out

of all genes with differentially methylated CpG site(s) for each of the three pesticides, we identified 712 genes (625 were hypermethylated and 87 were hypomethylated) overlapped for these three pesticides. Gene ontology analysis showed that these hyper- or hypo-methylated genes are implicated in carcinogenesis and related biological process, such as tumor protein p53 inducible protein 11 (TP53I11) (4.0-fold for fonofos, 4.7-fold for parathion, 3.1-fold for terbufos, respectively), growth arrest and DNA-damage-inducible gamma (GADD45G) (25.2-fold for fonofos, 23.1-fold for parathion, 31.2-fold for terbufos, respectively), and interleukin-1 receptor (IL1R1) (-2.2-fold for fonofos, -2.1-fold for parathion, -2.2 fold for terbufos, respectively). Our results provided direct experimental evidence that pesticides can modify DNA methylation in gene promoter CpG sites, which may play pathological role in cancer development. Further studies in other cell types and human samples are required before any firm conclusion could be reached on the significance of pesticide-induced methylation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Goodson, W. H., Lowe, L., Carpenter, D. O., Gilbertson, M., Ali, A. M., de Cerain Salsamendi, A. L., Lasfar, A., Carnero, A., Azqueta, A., Amedei, A., Charles, A. K., Collins, A. R., Ward, A., Salzberg, A. C., Colacci, A. M., Olsen, A. K., Berg, A., Barclay, B. J., Zhou, B. P., Blanco-Aparicio, C., Baglole, C. J., Dong, C., Mondello, C., Hsu, C. W., Naus, C. C., Yedjou, C., Curran, C. S., Laird, D. W., Koch, D. C., Carlin, D. J., Felsher, D. W., Roy, D., Brown, D. G., Ratovitski, E., Ryan, E. P., Corsini, E., Rojas, E., Moon, E. Y., Laconi, E., Marongiu, F., Al-Mulla, F., Chiaradonna, F., Darroudi, F., Martin, F. L., Van Schooten, F. J., Goldberg, G. S., Wagemaker, G., Nangami, G. N., Calaf, G. N., Williams, G. P., Wolf, G. T., Koppen, G., Brunborg, G., Kim Lyerly, H., Krishnan, H., Hamid, H. A., Yasaei, H., Sone, H., Kondoh, H., Salem, H. K., Hsu, H. Y., Park, H. H., Koturbash, I., Miousse, I. R., Ivana Scovassi, A., Klaunig, J. E., VondrÃ¡Ä?ek, J., Raju, J., Roman, J., Wise, J. P., Whitfield, J. R., Woodrick, J., Christopher, J. A., Ochieng, J., Martinez-Leal, J. F., Weisz, J., Kravchenko, J., Sun, J., Prudhomme, K. P., Narayanan, K. B., Cohen-Solal, K. A., Moorwood, K., Gonzalez, L., Soucek, L., Jian, L., D'Abronzo, L. S., Lin, L. T., Li, L., Gulliver, L., McCawley, L. J., Memeo, L., Vermeulen, L., Leyns, L., Zhang, L., Valverde, M., Khatami, M., Romano, M. F., Chapellier, M., Williams, M. A., Wade, M., Manjili, M. H., Lleonart, M. E., Xia, M., Guzman, M. J. G., Karamouzis, M. V., Kirsch-Volders, M., Vaccari, M., Kuemmerle, N. B., Singh, N., Cruickshanks, N., Kleinstreuer, N., van Larebeke, N., Ahmed, N., Ogunkua, O., Krishnakumar, P. K., Vadgama, P., Marignani, P. A., Ghosh, P. M., Ostrosky-Wegman, P., Thompson, P. A., Dent, P., Heneberg, P., Darbre, P., Leung, P. S., Nangia-Makker, P., Cheng, Q., Brooks Robey, R., Al-Temaimi, R., Roy, R., Andrade-Vieira, R., Sinha, R. K., Mehta, R., Vento, R., Di Fiore, R., Ponce-Cusi, R., Dornetshuber-Fleiss, R., Nahta, R., Castellino, R. C., Palorini, R., Hamid, R. A., Langie, S. A. S., Eltom, S. E., Brooks, S. A., Ryeom, S., Wise, S. S., Bay, S. N., Harris, S. A., Papagerakis, S., Romano, S., Pavanello, S., Eriksson, S., Forte, S., Casey, S. C., Luanpitpong, S., Lee, T. J., Otsuki, T., Chen, T., Massfelder, T., Sanderson, T., Guarnieri, T., Hultman, T., Dormoy, V., Odero-Marah, V., Sabbisetti, V., Maguer-Satta, V., Kimryn Rathmell, W., EngstrÃ¶m, W., Decker, W. K., Bisson, W. H., Rojanasakul, Y., Luqmani, Y., Chen, Z., Hu, Z.","Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: The challenge ahead","","36:S254-S296","4f28f07e-15ce-4fea-b9a5-dc7c1562fb16","","Lifestyle factors are responsible for a considerable portion of cancer incidence worldwide, but credible estimates from the World Health

Organization and the International Agency for Research on Cancer (IARC) suggest that the fraction of cancers attributable to toxic environmental exposures is between 7% and 19%. To explore the hypothesis that low-dose exposures to mixtures of chemicals in the environment may be combining to contribute to environmental carcinogenesis, we reviewed 11 hallmark phenotypes of cancer, multiple priority target sites for disruption in each area and prototypical chemical disruptors for all targets, this included dose-response characterizations, evidence of low-dose effects and cross-hallmark effects for all targets and chemicals. In total, 85 examples of chemicals were reviewed for actions on key pathways/mechanisms related to carcinogenesis. Only 15% (13/85) were found to have evidence of a dose-response threshold, whereas 59% (50/85) exerted low-dose effects. No dose-response information was found for the remaining 26% (22/85). Our analysis suggests that the cumulative effects of individual (non-carcinogenic) chemicals acting on different pathways, and a variety of related systems, organs, tissues and cells could plausibly conspire to produce carcinogenic synergies. Additional basic research on carcinogenesis and research focused on low-dose effects of chemical mixtures needs to be rigorously pursued before the merits of this hypothesis can be further advanced. However, the structure of the World Health Organization International Programme on Chemical Safety 'Mode of Action' framework should be revisited as it has inherent weaknesses that are not fully aligned with our current understanding of cancer biology.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1999","Josse, D., Xie, W., Masson, P., Schopfer, L. M., Lockridge, O.","Tryptophan residue(s) as major components of the human serum paraoxonase active site","Chemico-biological interactions","119-120:79-84","0dafceb7-3061-4aaf-881e-72ef6f419224","","Serum paraoxonase (PON1, EC 3.1.8.1.) is a high density lipid- (HDL)-associated, calcium-dependent enzyme whose 3D structure, active site residues and physiological substrates are not known. The kinetic parameters k(cat) and Km (relative to k(cat) and Km of the wild-type), determined with four substrates (phenylacetate, paraoxon, diazoxon and chlorpyrifosoxon) were less than 1, and more than 100% for the W280A and W280F mutant enzymes, respectively. These results indicated that the aromatic/hydrophobic character of the amino acid in position 280 is essential for PON1 activity. In this study, we investigated whether this aromatic residue is in the PON1 active site. Group-specific labelling studies with N-bromosuccinimide, an oxidative agent of tryptophan, strongly suggested that one or several Trp could be in the active site of PON1 but we could not conclude either on the specificity of the labelling reaction or on the number of oxidized Trp. However, although PON activity was not altered by the hydrophilic tryptophan-modifying reagent 2-hydroxy-5-nitrobenzyl chloride (NBC), it was significantly reduced by the p-nitrophenylacetate analog 2-acetoxy-5-nitrobenzyl chloride (ANBC), whose hydrolysis by PON1 generated NBC in the active site. Moreover, since at least one calcium ion is present in the PON catalytic site, we attempted to probe the metal local environment using the calcium analog terbium. The luminescence spectrum of the PON terbium complex exhibited an emission peak at 545 nm characteristic of an aromatic residue (Trp and/or Tyr)-terbium interaction. In conclusion, both the results obtained with the mechanism-based inhibitor of PON1 (ANBC) and the calcium-binding site luminescent probe terbium support the hypothesis of the presence of at least one Trp residue in the PON1 active site. Trp residue(s) may be involved in the binding of aromatic substrates.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","D'Agostino, J., Zhang, H.,

Kenaan, C., Hollenberg, P. F.","Mechanism-Based Inactivation of Human Cytochrome P450 2B6 by Chlorpyrifos","Chemical research in toxicology","28(7):1484-95","a8cbfd8a-91f8-42d0-b7b8-ffc28e18494b","","Chlorpyrifos (CPS) is a commonly used pesticide which is metabolized by P450s into the toxic metabolite chlorpyrifos-oxon (CPO). Metabolism also results in the release of sulfur, which has been suggested to be involved in mechanism-based inactivation (MBI) of P450s. CYP2B6 was previously determined to have the greatest catalytic efficiency for CPO formation in vitro. Therefore, we characterized the MBI of CYP2B6 by CPS. CPS inactivated CYP2B6 in a time- and concentration-dependent manner with a kinact of 1.97 min(-1), a KI of 0.47 muM, and a partition ratio of 17.7. We further evaluated the ability of other organophosphate pesticides including chorpyrifos-methyl, diazinon, parathion-methyl, and azinophos-methyl to inactivate CYP2B6. These organophosphate pesticides were also potent MBIs of CYP2B6 characterized by similar kinact and KI values. The inactivation of CYP2B6 by CPS was accompanied by the loss of P450 detectable in the CO reduced spectrum and loss of detectable heme. High molecular weight aggregates were observed when inactivated CYP2B6 was run on SDS-PAGE gels indicating protein aggregation. Interestingly, we found that the rat homologue of CYP2B6, CYP2B1, was not inactivated by CPS despite forming CPO to a similar extent. On the basis of the locations of the Cys residues in the two proteins which could react with released sulfur during the metabolism of CPS, we investigated whether the C475 in CYP2B6, which is not conserved in CYP2B1, was the critical residue for inactivation by mutating it to a Ser. CYP2B6 C475S was inactivated to a similar extent as wild type CYP2B6 indicating that C475 is not likely the key difference between CYP2B1 and CYP2B6 with respect to inactivation. These results indicate that CPS and other organophosphate pesticides are potent MBIs of CYP2B6 which may have implications for the toxicity of these pesticides as well as the potential for pesticide-drug interactions.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2015","Deferme, L., Wolters, J., Claessen, S., Briede, J., Kleinjans, J.","Oxidative Stress Mechanisms Do Not Discriminate between Genotoxic and Nongenotoxic Liver Carcinogens","Chemical research in toxicology","28(8):1636-46","58df50a9-9f63-4701-92f8-eb37872d512b","","It is widely accepted that in chemical carcinogenesis different modes-of-action exist, e.g., genotoxic (GTX) versus nongenotoxic (NGTX) carcinogenesis. In this context, it has been suggested that oxidative stress response pathways are typical for NGTX carcinogenesis. To evaluate this, we examined oxidative stress-related changes in gene expression, cell cycle distribution, and (oxidative) DNA damage in human hepatoma cells (HepG2) exposed to GTX-, NGTX-, and noncarcinogens, at multiple time points (4-8-24-48-72 h). Two GTX (azathriopine (AZA) and furan) and two NGTX (tetradecanoyl-phorbol-acetate, (TPA) and tetrachloroethylene (TCE)) carcinogens as well as two noncarcinogens (diazinon (DZN, d-mannitol (Dman)) were selected, while per class one compound was deemed to induce oxidative stress and the other not. Oxidative stressors AZA, TPA, and DZN induced a 10-fold higher number of gene expression changes over time compared to those of furan, TCE, or Dman treatment. Genes commonly expressed among AZA, TPA, and DZN were specifically involved in oxidative stress, DNA damage, and immune responses. However, differences in gene expression between GTX and NGTX carcinogens did not correlate to oxidative stress or DNA damage but could instead be assigned to compound-specific characteristics. This conclusion was underlined by results from functional readouts on ROS formation and (oxidative) DNA damage. Therefore, oxidative stress may represent the underlying cause for increased risk of liver toxicity and even carcinogenesis; however,

it does not discriminate between GTX and NGTX carcinogens.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2010","Aluigi, M. G., Guida, C., Falugi, C.","Apoptosis as a specific biomarker of diazinon toxicity in NTera2-D1 cells","","187(1-3):299-303","22039701-bd0b-440f-8121-2db3ac9502a6","","The NTera2/D1 (NT2) cell line, which was derived from a human teratocarcinoma, exhibits properties that are characteristics of a committed neuronal precursor at an early stage of differentiation. Its property to express a whole set of molecules related to the cholinergic neurotransmission system, including active acetylcholinesterase (AChE, EC 3.1.1.7) makes it a good alternative model for testing the effects of neurotoxic compounds, such as organophosphorus (OP) insecticides, whose primary target is the inhibition of AChE activity.Recent findings have elucidated the role of AChE in the modulation of apoptosis, but the mechanisms are still rather obscure.NT2 cells exposed to the OP insecticide diazinon at concentrations ranging between 10-4 and 10-5M showed a time-dependent enhancement of cell death. When exposed at 10-6M diazinon showed higher cell viability than control samples up to 72h, followed by a decreasing phase. The cell death caused by the exposures showed a number of features characteristic of apoptosis, including membrane and mitochondrial potential changes. We suggest the hypothesis that such behaviour is due to a dynamic balance between activated and blocked acetylcholine receptors that in turn trigger electrical events and caspase cascade. Â© 2010 Elsevier Ireland Ltd.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2006","Trielli, F., Chessa, M. G., Amaroli, A., Ognibene, M., Delmonte Corrado, M. U.","Effects of organophosphate compounds on a soil protist, Colpoda inflata (Ciliophora, Colpodidae)","Chemosphere","65(10):1731-7","ebf36969-6d6d-474f-bff5-c552ccb93af3","","Many investigations on protists indicate that they play an important role in agricultural soils. We have tested the effects of three organophosphate (OP) pesticides, basudin, cidial, and fenix, on the soil ciliate Colpoda inflata, and examined its viability, fission rate, ability to excyst and extrude macronuclear chromatin into cytoplasm. Exposure to these OPs caused a dose-dependent effect on cell viability, and significantly reduced the mean fission rate at a concentration of 1/10(5) v/v. After exposure of resting cysts to 1/10(5) v/v or 1/10(6) v/v concentrations of basudin or cidial, the number of excysted cells was significantly lower than that of the controls. Conversely, exposure to a 1/10(5) v/v fenix concentration did not affect excystment and exposure to 1/10(6) v/v was found to promote excystment. Moreover, exposure to these OPs (1/10(4) v/v or 1/10(5) v/v) interferred with the ability to extrude macronuclear chromatin. The median lethal concentration in 60 min for each OPs tested was at least a hundred times lower than the doses recommended by the manufacturer. Finally, as the inhibition of cholinesterase (ChE) activity is the first target of OPs, the presence of ChE activity was checked in C. inflata. Three ChE activities were found, hydrolyzing the substrates acetyl-beta-methyl thiocholine iodide, propionyl thiocholine iodide and butyryl thiocholine iodide, that appeared to be very low and not inhibited by OP-exposure.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2006","Borchers, A. T., Chang, C., Keen, C. L., Gershwin, M. E.","Airborne environmental injuries and human health","","31(1):1-101","9bbfca72-52e5-42e8-8e4a-215ad6ea7d0d","","The concept that the environment in which we live can have detrimental effects on our health has existed for centuries.

Obvious examples of substances that can cause human diseases include infectious agents, poisons, chemicals and other noxious agents, drugs, and physical stimuli such as bright lights and loud sounds. Some less obvious agents can include allergens, nontangible agents such as colorless, odorless gases and aerosolized toxins. In recent decades, humans have developed various new materials and compounds. Additionally, we are now producing known compounds, and even naturally occurring substances, in vastly increased amounts. Many of these substances are generally believed to threaten the health of our environment. However, there is also a considerable amount of hype and exaggeration regarding some of these agents (e.g., mold) that is unsubstantiated. This article extensively reviews the data on a large number of airborne-related illnesses and attempted to place scientific reality in the context of clinical medicine. ","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Jemec, A., Drobne, D., Tisler, T., Trebse, P., Ros, M., Sepcic, K.","The applicability of acetylcholinesterase and glutathione S-transferase in Daphnia magna toxicity test","Comparative biochemistry and physiology. Toxicology & pharmacology : CBP","144(4):303-9","88764140-d196-41d9-933b-bc87afcf8ae7","","The most commonly used toxicity test worldwide is the acute Daphnia magna test. The relevance of acetylcholinesterase (AChE) and glutathione S-transferase (GST) activity in D. magna exposed to chromium, cadmium, and diazinon was evaluated in connection with this standard test. We found no link between enzyme activities and immobility. Concentrations of Cr(6+) up to 280 microg/L had no effect on AChE and GST activities, while 20% immobility was observed. At concentrations of 20-25 microg/L of Cd(2+) AChE activity was increased by about 50%. The effect of diazinon on both enzymes was insignificant up to concentrations that caused 27% immobility. Consequently, while the use of AChE and GST activities is recommended when the mode of action of chemicals is studied, the value of these biomarkers in routine acute toxicity tests is limited because the relationship between enzyme activities and immobility of D. magna exposed to different chemicals is unclear.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Boobis, A., Budinsky, R., Collie, S., Crofton, K., Embry, M., Felter, S., Hertzberg, R., Kopp, D., Mihlan, G., Mumtaz, M., Price, P., Solomon, K., Teuschler, L., Yang, R., Zaleski, R.","Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment","","41(5):369-383","aab8d9df-80bd-4272-84ce-a49b2ceb69a3","","There is increasing interest in the use of tiered approaches in risk assessment of mixtures or co-exposures to chemicals for prioritization. One possible screening-level risk assessment approach is the threshold of toxicological concern (TTC). To date, default assumptions of dose or response additivity have been used to characterize the toxicity of chemical mixtures. Before a screening-level approach could be used, it is essential to know whether synergistic interactions can occur at low, environmentally relevant exposure levels. Studies demonstrating synergism in mammalian test systems were identified from the literature, with emphasis on studies performed at doses close to the points of departure (PODs) for individual chemicals. This search identified 90 studies on mixtures. Few included quantitative estimates of low-dose synergy; calculations of the magnitude of interaction were included in only 11 papers. Quantitative methodology varied across studies in terms of the null hypothesis, response measured, POD used to test for synergy, and consideration of the slope of the dose-response curve. It was concluded that consistent approaches should be applied for

quantification of synergy, including that synergy be defined in terms of departure from dose additivity; uniform procedures be developed for assessing synergy at low exposures; and the method for determining the POD for calculating synergy be standardized. After evaluation of the six studies that provided useful quantitative estimates of synergy, the magnitude of synergy at low doses did not exceed the levels predicted by additive models by more than a factor of 4. Â© 2011 Informa Healthcare USA, Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Doe, J. E., Boobis, A. R., Blacker, A., Dellarco, V., Doerrer, N. G., Franklin, C., Goodman, J. I., Kronenberg, J. M., Lewis, R., McConnell, E. E., Mercier, T., Moretto, A., Nolan, C., Padilla, S., Tilbury, L., Phang, W., Solecki, R., Van Ravenzwaay, B., Wolf, D. C.","A tiered approach to systemic toxicity testing for agricultural chemical safety assessment","","36(1):37-68","60358d5d-36af-46ec-a62d-f8d8207559b4","","A proposal has been developed by the Agricultural Chemical Safety Assessment (ACSA) Technical Committee of the ILSI Health and Environmental Sciences Institute (HESI) for an improved approach to assessing the safety of crop protection chemicals. The goal is to ensure that studies are scientifically appropriate and necessary without being redundant, and that tests emphasize toxicological endpoints and exposure durations that are relevant for risk assessment. The ACSA Systemic Toxicity Task Force proposes an approach to systemic toxicity testing as one part of the overall assessment of a compound's potential to cause adverse effects on health. The approach is designed to provide more relevant data for deriving reference doses for shorter time periods of human exposure, and includes fewer studies for deriving longer term reference doses - that is, neither a 12-month dog study nor a mouse carcinogenicity study is recommended. All available data, including toxicokinetics and metabolism data and life stages information, are taken into account. The proposed tiered testing approach has the potential to provide new risk assessment information for shorter human exposure durations while reducing the number of animals used and without compromising the sensitivity of the determination of longer term reference doses. Copyright Â© Taylor and Francis Group, LLC.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Abdel-Daim, M. M.","Synergistic protective role of ceftriaxone and ascorbic acid against subacute diazinon-induced nephrotoxicity in rats","","","515c485f-4b04-407c-86c9-c26d55a8b520","","Diazinon (DZN) is a synthetic organophosphrus acaricide and insecticide widely used for veterinary and agricultural purposes. However, its animal and human exposure leads to nephrotoxicity. Our experimental objective was to evaluate protective effects of ceftriaxone and/or ascorbic acid-vitamin C against DZN-induced renal injury in male Wistar albino rats. DZN-treated animals revealed significant elevation in serum biochemical parameters related to renal injury: urea, uric acid and creatinine. DZN intoxication significantly increased renal lipid peroxidation, and significant inhibition in antioxidant biomarkers including, reduced glutathione, glutathione peroxidase, superoxide dismutase, catalase and total antioxidant capacity. In addition, DZN significantly reduced serum acetylcholinestrase level. Moreover, It induced serum and kidney tumor necrosis factor-Î± level. Both ceftriaxone and vitamin C protect against DZN-induced serum as well as renal tissue biochemical parameters when used alone or in combination along with DZN-intoxication. Furthermore, both ceftriaxone and vitamin C produced synergetic nephroprotective and antioxidant effects. Therefore, it could be concluded that ceftriaxone and/or vitamin C administration are able to minimize the toxic effects

of DZN by its free radical-scavenging and potent antioxidant activity. Â© 2014 Springer Science+Business Media Dordrecht.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2016","Abdel-Daim, M. M.","Synergistic protective role of ceftriaxone and ascorbic acid against subacute diazinon-induced nephrotoxicity in rats","","68(2):279-289","a1e7897b-55a9-430a-8b57-fb6903afb490","","Diazinon (DZN) is a synthetic organophosphrus acaricide and insecticide widely used for veterinary and agricultural purposes. However, its animal and human exposure leads to nephrotoxicity. Our experimental objective was to evaluate protective effects of ceftriaxone and/or ascorbic acidâ€"vitamin C against DZN-induced renal injury in male Wistar albino rats. DZN-treated animals revealed significant elevation in serum biochemical parameters related to renal injury: urea, uric acid and creatinine. DZN intoxication significantly increased renal lipid peroxidation, and significant inhibition in antioxidant biomarkers including, reduced glutathione, glutathione peroxidase, superoxide dismutase, catalase and total antioxidant capacity. In addition, DZN significantly reduced serum acetylcholinestrase level. Moreover, It induced serum and kidney tumor necrosis factor-Î± level. Both ceftriaxone and vitamin C protect against DZN-induced serum as well as renal tissue biochemical parameters when used alone or in combination along with DZN-intoxication. Furthermore, both ceftriaxone and vitamin C produced synergetic nephroprotective and antioxidant effects. Therefore, it could be concluded that ceftriaxone and/or vitamin C administration are able to minimize the toxic effects of DZN by its free radical-scavenging and potent antioxidant activity.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2015","Papadakis, E. N., Vryzas, Z., Kotopoulou, A., Kintzikoglou, K., Makris, K. C., Papadopoulou-Mourkidou, E.","A pesticide monitoring survey in rivers and lakes of northern Greece and its human and ecotoxicological risk assessment","","116:1-9","8598ee49-244a-4dbe-8cae-acf648a65844","","A pesticide monitoring study covering the main rivers and lakes of Northern Greece (Macedonia, Thrace and Thessaly) was undertaken. A total of 416 samples were collected over a 1.5-year sampling period (September 1999- February 2001) from six rivers and ten lakes. The water samples were analyzed with an off-line solid phase extraction technique coupled with a gas chromatography ion trap mass spectrometer using an analytical method for 147 pesticides and their metabolites, including organochlorines, organophosphates, triazines, chloroacetanilides, pyrethroids, carbamates, phthalimides and other pesticides (herbicides, insecticides and fungicides). Based on the pesticide survey results, a human health carcinogenic and non-carcinogenic risk assessment was conducted for adults and children. Ecotoxicological risk assessment was also conducted using default endpoint values and the risk quotient method. Results showed that the herbicides metolachlor, prometryn, alachlor and molinate, were the most frequently detected pesticides (29%, 12.5%, 12.5% and 10%, respectively). They also exhibited the highest concentration values, often exceeding 1. Î¼g/L. Chlorpyrifos ethyl was the most frequently detected insecticide (7%). Seasonal variations in measured pesticide concentrations were observed in all rivers and lakes. The highest concentrations were recorded during May-June period, right after pesticide application. Concentrations of six pesticides were above the maximum allowable limit of 0.1. Î¼g/L set for drinking water. Alachlor, atrazine and a-HCH showed unacceptable carcinogenic risk estimates (4.5E-06, 4.6E-06 and 1.3E-04, respectively). Annual average concentrations of chlorpyriphos ethyl (0.031. Î¼gL), dicofol (0.01. Î¼g/L), dieldrin (0.02. Î¼g/L) and endosulfan a (0.065. Î¼g/L) exceeded

the EU environmental quality standards. The risk quotient estimates for the insecticides chorpyrifos ethyl, diazinon and parathion methyl and herbicide prometryn were above acceptable risk values. The coupling of monitoring data to probabilistic human and ecotoxicological risk estimates could find use by Greek regulatory authorities, proposing effective pollution management schemes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Deziel, N. C., Colt, J. S., Kent, E. E., Gunier, R. B., Reynolds, P., Booth, B., Metayer, C., Ward, M. H.","Associations between self-reported pest treatments and pesticide concentrations in carpet dust","Environmental health : a global access science source","14:27","40c00ef8-e53c-4ef3-9374-e542a23b89fd","","BACKGROUND: Recent meta-analyses demonstrate an association between self-reported residential pesticide use and childhood leukemia risk. Self-reports may suffer from recall bias and provide information only on broad pesticide categories. We compared parental self-reported home and garden pest treatments to pesticides measured in carpet dust. METHODS: Parents of 277 children with leukemia and 306 controls in Northern and Central California (2001-2007) were asked about insect and weed treatments during the previous year. Carpet dust samples were analyzed for 47 pesticides. We present results for the 7 insecticides (carbaryl, propoxur, chlorpyrifos, diazinon, cyfluthrin, cypermethrin, permethrin), 5 herbicides (2,4-dichlorophenoxyacetic acid [2,4-D], chlorthal, dicamba, mecoprop, simazine), and 1 synergist (piperonyl butoxide) that were present in home and garden products during the study period and were detected in >/=25% of carpet dust samples. We constructed linear regression models for the relative change in pesticide concentrations associated with self-reported treatment of pest types in cases and controls separately and combined, adjusting for demographics, housing characteristics, and nearby agricultural pesticide applications. RESULTS: Several self-reported treatments were associated with pesticide concentrations in dust. For example, households with flea/tick treatments had 2.3 (95% Confidence Interval [CI]: 1.4, 3.7) times higher permethrin concentrations than households not reporting this treatment. Households reporting treatment for ants/cockroaches had 2.5 (95% CI: 1.5, 4.2) times higher cypermethrin levels than households not reporting this treatment. Weed treatment by a household member was associated with 1.9 (1.4, 2.6), 2.2 (1.6, 3.1), and 2.8 (2.1, 3.7) times higher dust concentrations of dicamba, mecoprop, and 2,4-D, respectively. Weed treatments by professional applicators were null/inversely associated with herbicide concentrations in dust. Associations were generally similar between cases and controls and were consistent with pesticide active ingredients in these products during the study time period. CONCLUSIONS: Consistency between self-reported pest treatments, concentrations in dust, and pesticides in products lends credibility to the exposure assessment methods and suggests that differential recall by case-control status is minimal.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D. P., Kamel, F.","Pesticide exposure and depression among male private pesticide applicators in the agricultural health study","Environmental health perspectives","122(9):984-91","9d1437b2-4a57-4218-ba00-b306c255ec77","","BACKGROUND: Pesticide exposure may be positively associated with depression. Few previous studies have considered the episodic nature of depression or examined individual pesticides. OBJECTIVE: We evaluated associations between pesticide exposure and depression among male private

pesticide applicators in the Agricultural Health Study. METHODS: We analyzed data for 10 pesticide classes and 50 specific pesticides used by 21,208 applicators enrolled in 1993-1997 who completed a follow-up telephone interview in 2005-2010. We divided applicators who reported a physician diagnosis of depression (n = 1,702; 8%) into those who reported a previous diagnosis of depression at enrollment but not follow-up (n = 474; 28%), at both enrollment and follow-up (n = 540; 32%), and at follow-up but not enrollment (n = 688; 40%) and used polytomous logistic regression to estimate odds ratios (ORs) and 95% CIs. We used inverse probability weighting to adjust for potential confounders and to account for the exclusion of 3,315 applicators with missing covariate data and 24,619 who did not complete the follow-up interview. RESULTS: After weighting for potential confounders, missing covariate data, and dropout, ever-use of two pesticide classes, fumigants and organochlorine insecticides, and seven individual pesticides-the fumigants aluminum phosphide and ethylene dibromide; the phenoxy herbicide (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T); the organochlorine insecticide dieldrin; and the organophosphate insecticides diazinon, malathion, and parathion-were all positively associated with depression in each case group, with ORs between 1.1 and 1.9. CONCLUSIONS: Our study supports a positive association between pesticide exposure and depression, including associations with several specific pesticides.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Gunier, R. B., Ward, M. H., Airola, M., Bell, E. M., Colt, J., Nishioka, M., Buffler, P. A., Reynolds, P., Rull, R. P., Hertz, A., Metayer, C., Nuckols, J. R.","Determinants of agricultural pesticide concentrations in carpet dust","Environmental health perspectives","119(7):970-6","e614a633-35a2-46cd-8dd6-a05bbb399556","","BACKGROUND: Residential proximity to agricultural pesticide applications has been used as a surrogate for exposure in epidemiologic studies, although little is known about the relationship with levels of pesticides in homes. OBJECTIVE: We identified determinants of concentrations of agricultural pesticides in dust. METHODS: We collected samples of carpet dust and mapped crops within 1,250 m of 89 residences in California. We measured concentrations of seven pesticides used extensively in agriculture (carbaryl, chlorpyrifos, chlorthal-dimethyl, diazinon, iprodione, phosmet, and simazine). We estimated use of agricultural pesticides near residences from a statewide database alone and by linking the database with crop maps. We calculated the density of pesticide use within 500 and 1,250 m of residences for 180, 365, and 730 days before collection of dust and evaluated relationships between agricultural pesticide use estimates and pesticide concentrations in carpet dust. RESULTS: For five of the seven pesticides evaluated, residences with use of agricultural pesticides within 1,250 m during the previous 365 days had significantly higher concentrations of pesticides than did residences with no nearby use. The highest correlation with concentrations of pesticides was generally for use reported within 1,250 m of the residence and 730 days before sample collection. Regression models that also accounted for occupational and home use of pesticides explained only a modest amount of the variability in pesticide concentrations (4-28%). CONCLUSIONS: Agricultural pesticide use near residences was a significant determinant of concentrations of pesticides in carpet dust for five of seven pesticides evaluated.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Jameson, R. R., Seidler, F. J., Slotkin, T. A.","Nonenzymatic functions of acetylcholinesterase splice variants in the developmental neurotoxicity of organophosphates: chlorpyrifos, chlorpyrifos oxon, and

diazinon","Environmental health perspectives","115(1):65-70","e1529e4b-a78c-4bf9-ba39-02fb37f72853","","BACKGROUND: Organophosphate pesticides affect mammalian brain development through mechanisms separable from the inhibition of acetylcholinesterase (AChE) enzymatic activity and resultant cholinergic hyperstimulation. In the brain, AChE has two catalytically similar splice variants with distinct functions in development and repair. The rare, read-through isoform, AChE-R, is preferentially induced by injury and appears to promote repair and protect against neurodegeneration. Overexpression of the more abundant, synaptic isoform, AChE-S, enhances neurotoxicity. OBJECTIVES: We exposed differentiating PC12 cells, a model for developing neurons, to 30 microM chlorpyrifos (CPF) or diazinon (DZN), or CPF oxon, the active metabolite that irreversibly inhibits AChE enzymatic activity, in order to determine whether they differentially induce the formation of AChE-S as a mechanistic predictor of developmental neurotoxicity. We then administered CPF or DZN to neonatal rats on postnatal days 1-4 using daily doses spanning the threshold for AChE inhibition (0-20%); we then evaluated AChE gene expression in forebrain and brainstem on post-natal day 5. RESULTS: In PC12 cells, after 48 hr of exposure, CPF, CPF oxon, and DZN enhanced gene expression for AChE-R by about 20%, whereas CPF and DZN, but not CPF oxon, increased AChE-S expression by 20-40%. Thus, despite the fact that CPF oxon is a much more potent AChE inhibitor, it is the native compound (CPF) that induces expression of the neurotoxic AChE-S isoform. For in vivo exposures, 1 mg/kg CPF had little or no effect, but 0.5 or 2 mg/kg DZN induced both AChE-R and AChE-S, with a greater effect in males. CONCLUSIONS: Our results indicate that nonenzymatic functions of AChE variants may participate in and be predictive of the relative developmental neurotoxicity of organophosphates, and that the various organophosphates differ in the degree to which they activate this mechanism.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2002","Lee, S., McLaughlin, R., Harnly, M., Gunier, R., Kreutzer, R.","Community exposures to airborne agricultural pesticides in California: ranking of inhalation risks","Environmental health perspectives","110(12):1175-84","160a66d7-0ce2-41a4-a708-6e7bc4e9176f","","We assessed inhalation risks to California communities from airborne agricultural pesticides by probability distribution analysis using ambient air data provided by the California Air Resources Board and the California Department of Pesticide Regulation. The pesticides evaluated include chloropicrin, chlorothalonil, chlorpyrifos, S,S,S-tributyl phosphorotrithioate, diazinon, 1,3-dichloropropene, dichlorvos (naled breakdown product), endosulfan, eptam, methidathion, methyl bromide, methyl isothiocyanate (MITC; metam sodium breakdown product), molinate, propargite, and simazine. Risks were estimated for the median and 75th and 95th percentiles of probability (50, 25, and 5% of the exposed populations). Exposure estimates greater than or equal to noncancer reference values occurred for 50% of the exposed populations (adults and children) for MITC subchronic and chronic exposures, methyl bromide subchronic exposures (year 2000 monitoring), and 1,3-dichloropropene subchronic exposures (1990 monitoring). Short-term chlorpyrifos exposure estimates exceeded the acute reference value for 50% of children (not adults) in the exposed population. Noncancer risks were uniformly higher for children due to a proportionately greater inhalation rate-to-body weight ratio compared to adults and other factors. Target health effects of potential concern for these exposures include neurologic effects (methyl bromide and chlorpyrifos) and respiratory effects (1,3-dichloropropene and MITC). The lowest noncancer risks occurred for simazine and chlorothalonil. Lifetime cancer risks of one-in-a-million or greater were

estimated for 50% of the exposed population for 1,3-dichloropropene (1990 monitoring) and 25% of the exposed populations for methidathion and molinate. Pesticide vapor pressure was found to be a better predictor of inhalation risk compared to other methods of ranking pesticides as potential toxic air contaminants.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2001","Qiao, D., Seidler, F. J., Slotkin, T. A.","Developmental neurotoxicity of chlorpyrifos modeled in vitro: comparative effects of metabolites and other cholinesterase inhibitors on DNA synthesis in PC12 and C6 cells","Environmental health perspectives","109(9):909-13","fd08728a-d924-4a53-9974-8f9dfe0d99dc","","The widely used organophosphate pesticide chlorpyrifos is a suspected neuroteratogen. In the current study, we compared the effects of chlorpyrifos and its major metabolites in two in vitro models, neuronotypic PC12 cells and gliotypic C6 cells. Chlorpyrifos inhibited DNA synthesis in both cell lines but had a greater effect on gliotypic cells. Chlorpyrifos oxon, the active metabolite that inhibits cholinesterase, also decreased DNA synthesis in PC12 and C6 cells with a preferential effect on the latter. Trichloropyridinol, the major catabolic product of chlorpyrifos, had a much smaller, but nevertheless statistically significant, effect that was equivalent in both cell lines. Diazinon, another organophosphate pesticide, also inhibited DNA synthesis with preference toward C6 cells, but was less effective than was chlorpyrifos. Physostigmine, a non-organophosphate cholinesterase inhibitor, was less effective than either chlorpyrifos or diazinon, but still caused significant inhibition of DNA synthesis in C6 cells. We also found that the addition of sera protected the cells from the adverse effects of chlorpyrifos and that the effect could be reproduced by addition of albumin. These results indicate that chlorpyrifos and other organophosphates such as diazinon have immediate, direct effects on neural cell replication, preferentially for gliotypic cells. In light of the protective effect of serum proteins, the fact that the fetus and newborn possess lower concentrations of these proteins suggests that greater neurotoxic effects may occur at blood levels of chlorpyrifos that are nontoxic to adults.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2005","Searles Nielsen, S., Mueller, B. A., De Roos, A. J., Viernes, H. M., Farin, F. M., Checkoway, H.","Risk of brain tumors in children and susceptibility to organophosphorus insecticides: the potential role of paraoxonase (PON1)","Environmental health perspectives","113(7):909-13","bf127b5f-f745-4622-8e14-4f5fbabcd728","","Prior research suggests that childhood brain tumors (CBTs) may be associated with exposure to pesticides. Organophosphorus insecticides (OPs) target the developing nervous system, and until recently, the most common residential insecticides were chlorpyrifos and diazinon, two OPs metabolized in the body through the cytochrome P450/paraoxonase 1 (PON1) pathway. To investigate whether two common PON1 polymorphisms, C-108T and Q192R, are associated with CBT occurrence, we conducted a population-based study of 66 cases and 236 controls using DNA from neonatal screening archive specimens in Washington State, linked to interview data. The risk of CBT was nonsignificantly increased in relation to the inefficient PON1 promoter allele [per PON1(-108T) allele, relative to PON1(-108CC): odds ratio (OR) = 1.4; 95% confidence interval (CI), 1.0-2.2; p-value for trend = 0.07]. Notably, this association was strongest and statistically significant among children whose mothers reported chemical treatment of the home for pests during pregnancy or childhood (per PON1(-108T) allele: among exposed, OR = 2.6; 95% CI, 1.2-5.5; among unexposed, OR = 0.9; 95% CI, 0.5-1.6) and for primitive neuroectodermal tumors (per PON1(-108T) allele: OR = 2.4; 95% CI,

1.1-5.4). The Q192R polymorphism, which alters the structure of PON1 and influences enzyme activity in a substrate-dependent manner, was not associated with CBT risk, nor was the PON1(C-108T/Q192R) haplotype. These results are consistent with an inverse association between PON1 levels and CBT occurrence, perhaps because of PON1's ability to detoxify OPs common in children's environments. Larger studies that measure plasma PON1 levels and incorporate more accurate estimates of pesticide exposure will be required to confirm these observations.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2007","Slotkin, T. A., MacKillop, E. A., Ryde, I. T., Tate, C. A., Seidler, F. J.","Screening for developmental neurotoxicity using PC12 cells: comparisons of organophosphates with a carbamate, an organochlorine, and divalent nickel","Environmental health perspectives","115(1):93-101","bc2bfc55-de8e-46ee-b9f6-d249b8a489da","","BACKGROUND: In light of the large number of chemicals that are potential developmental neurotoxicants, there is a need to develop rapid screening techniques. OBJECTIVES: We exposed undifferentiated and differentiating neuronotypic PC12 cells to different organophosphates (chlorpyrifos, diazinon, parathion), a carbamate (physostigmine), an organochlorine (dieldrin), and a metal (divalent nickel; Ni2+) and examined indices of cell replication and differentiation for both short- and long-term exposures. RESULTS: In undifferentiated cells, all the agents inhibited DNA synthesis, with the greatest effect for diazinon, but physostigmine eventually produced the largest deficits in the total number of cells after prolonged exposure. The onset of differentiation intensified the adverse effects on DNA synthesis and changed the rank order in keeping with a shift away from noncholinergic mechanisms and toward cholinergic mechanisms. Differentiation also worsened the effects of each agent on cell number after prolonged exposure, whereas cell growth was not suppressed, nor were there any effects on viability as assessed with trypan blue. Nevertheless, differentiating cells displayed signs of oxidative stress from all of the test compounds except Ni2+, as evidenced by measurements of lipid peroxidation. Finally, all of the toxicants shifted the transmitter fate of the cells away from the cholinergic phenotype and toward the catecholaminergic phenotype. CONCLUSIONS: These studies point out the feasibility of developing cell-based screening methods that enable the detection of multiple end points that may relate to mechanisms associated with developmental neurotoxicity, revealing some common targets for disparate agents.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2009","Slotkin, T. A., Seidler, F. J.","Oxidative and excitatory mechanisms of developmental neurotoxicity: transcriptional profiles for chlorpyrifos, diazinon, dieldrin, and divalent nickel in PC12 cells","Environmental health perspectives","117(4):587-96","893f217e-8ac1-4ffa-8ecb-33e65c659d17","","BACKGROUND: Oxidative stress and excitotoxicity underlie the developmental neurotoxicity of numerous chemicals. OBJECTIVES: We compared the effects of organophosphates (chlorpyrifos and diazinon), an organo-chlorine (dieldrin), and a metal [divalent nickel (Ni2+)] to determine how these mechanisms contribute to similar or dissimilar neurotoxic outcomes. METHODS: We used PC12 cells as a model of developing neurons and evaluated transcriptional profiles for genes for oxidative stress responses and glutamate receptors. RESULTS: Chlorpyrifos had a greater effect on oxidative-stress-related genes in differentiating cells compared with the undifferentiated state. Chlorpyrifos and diazinon showed significant concordance in their effects on glutathione-related genes, but they were negatively correlated for effects on catalase and superoxide dismutase isoforms and had no concordance for effects on ionotropic

glutamate receptors. Surprisingly, the correlations were stronger between diazinon and dieldrin than between the two organophosphates. The effects of Ni2+ were the least similar for genes related to oxidative stress but had significant concordance with dieldrin for effects on glutamate receptors. CONCLUSIONS: Our results point to underlying mechanisms by which different organophosphates produce disparate neurotoxic outcomes despite their shared property as cholinesterase inhibitors. Further, apparently unrelated neurotoxicants may produce similar outcomes because of convergence on oxidative stress and excitotoxicity. The combined use of cell cultures and microarrays points to specific end points that can distinguish similarities and disparities in the effects of diverse developmental neurotoxicants.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Weichenthal, S., Moase, C., Chan, P.","A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort","Environmental health perspectives","118(8):1117-25","ddaa28e7-f4a0-4c7d-8b87-acd3ae376d86","","OBJECTIVE: We reviewed epidemiologic evidence related to occupational pesticide exposures and cancer incidence in the Agricultural Health Study (AHS) cohort. DATA SOURCES: Studies were identified from the AHS publication list available at http://aghealth.nci.nih.gov as well as through a Medline/PubMed database search in March 2009. We also examined citation lists. Findings related to lifetime-days and/or intensity-weighted lifetime-days of pesticide use are the primary focus of this review, because these measures allow for the evaluation of potential exposure-response relationships. DATA SYNTHESIS: We reviewed 28 studies; most of the 32 pesticides examined were not strongly associated with cancer incidence in pesticide applicators. Increased rate ratios (or odds ratios) and positive exposure-response patterns were reported for 12 pesticides currently registered in Canada and/or the United States (alachlor, aldicarb, carbaryl, chlorpyrifos, diazinon, dicamba, S-ethyl-N,N-dipropylthiocarbamate, imazethapyr, metolachlor, pendimethalin, permethrin, trifluralin). However, estimates of association for specific cancers were often imprecise because of small numbers of exposed cases, and clear monotonic exposure-response patterns were not always apparent. Exposure misclassification is also a concern in the AHS and may limit the analysis of exposure-response patterns. Epidemiologic evidence outside the AHS remains limited with respect to most of the observed associations, but animal toxicity data support the biological plausibility of relationships observed for alachlor, carbaryl, metolachlor, pendimethalin, permethrin, and trifluralin. CONCLUSIONS: Continued follow-up is needed to clarify associations reported to date. In particular, further evaluation of registered pesticides is warranted.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Zhang, X., Wallace, A. D., Du, P., Kibbe, W. A., Jafari, N., Xie, H., Lin, S., Baccarelli, A., Soares, M. B., Hou, L.","DNA methylation alterations in response to pesticide exposure in vitro","Environmental and molecular mutagenesis","53(7):542-9","7de68945-d06d-4874-a956-007421af2fdb","","Although pesticides are subject to extensive carcinogenicity testing before regulatory approval, pesticide exposure has repeatedly been associated with various cancers. This suggests that pesticides may cause cancer via nonmutagenicity mechanisms. The present study provides evidence to support the hypothesis that pesticide-induced cancer may be mediated in part by epigenetic mechanisms. We examined whether exposure to seven commonly used pesticides (i.e., fonofos, parathion, terbufos, chlorpyrifos, diazinon, malathion, and phorate) induces

DNA methylation alterations in vitro. We conducted genome-wide DNA methylation analyses on DNA samples obtained from the human hematopoietic K562 cell line exposed to ethanol (control) and several organophosphate pesticides (OPs) using the Illumina Infinium HumanMethylation27 BeadChip. Bayesian-adjusted t-tests were used to identify differentially methylated gene promoter CpG sites. In this report, we present our results on three pesticides (fonofos, parathion, and terbufos) that clustered together based on principle component analysis and hierarchical clustering. These three pesticides induced similar methylation changes in the promoter regions of 712 genes, while also exhibiting their own OP-specific methylation alterations. Functional analysis of methylation changes specific to each OP, or common to all three OPs, revealed that differential methylation was associated with numerous genes that are involved in carcinogenesis-related processes. Our results provide experimental evidence that pesticides may modify gene promoter DNA methylation levels, suggesting that epigenetic mechanisms may contribute to pesticide-induced carcinogenesis. Further studies in other cell types and human samples are required, as well as determining the impact of these methylation changes on gene
expression.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Wofford, P., Segawa, R., Schreider, J., Federighi, V., Neal, R., Brattesani, M.","Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year","Environmental monitoring and assessment","186(3):1355-70","30acdcfb-37ae-4f7d-bac8-8d844efbda4f","","The CA Department of Pesticide Regulation (CDPR) and the CA Air Resources Board monitored 40 pesticides, including five degradation products, in Parlier, CA, to determine if its residents were exposed to any of these pesticides and, if so, in what amounts. They included 1,3-dichloropropene, acrolein, arsenic, azinphos-methyl, carbon disulfide, chlorpyrifos and its degradation product, chlorthalonil, copper, cypermethrin, diazinon and its degradation product, dichlorvos, dicofol, dimethoate and its degradation product, diuron, endosulfan and its degradation product, S-ethyl dipropylcarbamothioate (EPTC), formaldehyde, malathion and its degradation product, methyl isothiocyanate (MITC), methyl bromide, metolachlor, molinate, norflurazon, oryzalin, oxyfluorfen, permethrin, phosmet, propanil, propargite, simazine, SSS-tributylphosphorotrithioate, sulfur, thiobencarb, trifluralin, and xylene. Monitoring was conducted 3 days per week for a year. Twenty-three pesticides and degradation products were detected. Acrolein, arsenic, carbon disulfide, chlorpyrifos, copper, formaldehyde, methyl bromide, MITC, and sulfur were detected in more than half the samples. Since no regulatory ambient air standards exist for these pesticides, CDPR developed advisory, health-based non-cancer screening levels (SLs) to assess acute, subchronic, and chronic exposures. For carcinogenic pesticides, CDPR assessed risk using cancer potency values. Amongst non-carcinogenic agricultural use pesticides, only diazinon exceeded its SL. For carcinogens, 1,3-dichloropropene concentrations exceeded its cancer potency value. Based on these findings, CDPR has undertaken a more comprehensive evaluation of 1,3-dichloropropene, diazinon, and the closely related chlorpyrifos that was frequently detected. Four chemicals-acrolein, arsenic, carbon disulfide, and formaldehyde-sometimes used as pesticides were detected, although no pesticidal use was reported in the area during this study. Their presence was most likely due to vehicular or industrial
emissions.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Ukpebor, J., Llabjani, V.,

Martin, F. L., Halsall, C. J.","Sublethal genotoxicity and cell alterations by organophosphorus pesticides in MCF-7 cells: implications for environmentally relevant concentrations","Environmental toxicology and chemistry / SETAC","30(3):632-9","1ae7ad1a-cd07-4ce5-bef3-f4ca2ca08ce6","","Organophosphorus pesticide (OPP) toxicity is believed to be mediated through inhibition of acetylcholinesterase (AChE). Given their widespread distribution in aquatic systems and their ability to undergo chemical transformation, their environmental impacts at sublethal concentrations in nontarget organisms have become an important question. We conducted a number of mammalian-cell genotoxic and gene expression assays and examined cellular biochemical changes that followed low-dose exposure of MCF-7 cells to fenitrothion, diazinon, and the aqueous degradate of diazinon, 2-isopropyl-6-methyl-4-pyrimidinol (IMP). After exposure to the OPPs at low concentrations (10(-12) M to 10(-8) M), greater than twofold elevations in micronucleus formation were noted in MCF-7 cell cultures that went on to exhibit greater than 75% clonogenic survival; these levels of chromosomal damage were comparable to those induced by 10(-6) M benzo[a]pyrene, a known genotoxic agent. At this low concentration range, a fenitrothion-induced twofold elevation in B-cell leukemia/lymphoma-2 (BCL-2) and cytochrome P450 isoenzyme (CYP1A1) gene expressions was observed. Principal component analysis-linear discriminant analysis (PCA-LDA) of derived infrared (IR) spectra of vehicle control (nonexposed) and OPP-exposed cells highlighted that both fenitrothion and diazinon induced marked biochemical alterations in the lipid, protein, and DNA/RNA absorbance regions. Our findings demonstrate that the two OPP parent chemicals and IMP degradate can mediate a number of toxic effects or cellular alterations at very low concentrations. These are independent of just selective inhibition of AChE, with potential consequences for nontarget organisms exposed at environmentally relevant concentrations. Further assays on relevant aquatic organism cell lines are now recommended to understand the mechanistic low-dose toxicity of these chemicals present in aquatic systems.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2012","Zhang, X., Wallace, A. D., Du, P., Lin, S., Baccarelli, A. A., Jiang, H., Jafari, N., Zheng, Y., Xie, H., Soares, M. B., Kibbe, W. A., Hou, L.","Genome-wide study of DNA methylation alterations in response to diazinon exposure in vitro","Environmental toxicology and pharmacology","34(3):959-68","8a14f0d0-5463-49fc-92f8-1e24f65c59a0","","Pesticide exposure has repeatedly been associated with cancers. However, molecular mechanisms are largely undetermined. In this study, we examined whether exposure to diazinon, a common organophosphate that has been associated with cancers, could induce DNA methylation alterations. We conducted genome-wide DNA methylation analyses on DNA samples obtained from human hematopoietic K562 cell exposed to diazinon and ethanol using the Illumina Infinium HumanMethylation27 BeadChip. Bayesian-adjusted t-tests were used to identify differentially methylated gene promoter CpG sites. We identified 1069 CpG sites in 984 genes with significant methylation changes in diazinon-treated cells. Gene ontology analysis demonstrated that some genes are tumor suppressor genes, such as TP53INP1 (3.0-fold, q-value <0.001) and PTEN (2.6-fold, q-value <0.001), some genes are in cancer-related pathways, such as HDAC3 (2.2-fold, q-value=0.002), and some remain functionally unknown. Our results provided direct experimental evidence that diazinon may modify gene promoter DNA methylation levels, which may play a pathological role in cancer development.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2011","Barry, K. H., Koutros, S.,

Berndt, S. I., Andreotti, G., Hoppin, J. A., Sandler, D. P., Burdette, L. A., Yeager, M., Freeman, L. E. B., Lubin, J. H., Ma, X., Zheng, T., Alavanja, M. C. R.","Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk","","119(12):1726-1732","d9b98cf9-1706-4956-8ff5-52a33936585d","","Background: Previous research indicates increased prostate cancer risk for pesticide applicators and pesticide manufacturing workers. Although underlying mechanisms are unknown, evidence suggests a role of oxidative DNA damage. Objectives: Because base excision repair (BER) is the predominant pathway involved in repairing oxidative damage, we evaluated interactions between 39 pesticides and 394 tag single-nucleotide polymorphisms (SNPs) for 31 BER genes among 776 prostate cancer cases and 1,444 male controls in a nested case-control study of white Agricultural Health Study (AHS) pesticide applicators. Methods: We used likelihood ratio tests from logistic regression models to determine p-values for interactions between three-level pesticide exposure variables (none/low/high) and SNPs (assuming a dominant model), and the false discovery rate (FDR) multiple comparison adjustment approach. Results: The interaction between fonofos and rs1983132 in NEIL3 [nei endonuclease VIII-like 3 (Escherichia coli)], which encodes a glycosylase that can initiate BER, was the most significant over-all [interaction p-value (pinteract) = 9.3 Ã- 10-6; FDR-adjusted p-value = 0.01]. Fonofos exposure was associated with a monotonic increase in prostate cancer risk among men with CT/TT genot{stroke}types for rs1983132 [odds ratios (95% confidence intervals) for low and high use compared with no use were 1.65 (0.91, 3.01) and 3.25 (1.78, 5.92), respectively], whereas fonofos was not associated with prostate cancer risk among men with the CC genot{stroke}type. Carbofuran and S-ethyl dipropylt{stroke}hiocarbamate (EPTC) interacted similarly with rs1983132; however, these interactions did not meet an FDR < 0.2. Conclusions: Our significant finding regarding fonofos is consistent with previous AHS findings of increased prostate cancer risk with fonofos exposure among those with a family history of prostate cancer. Although requiring replication, our findings suggest a role of BER genetic variation in pesticide-associated prostate cancer risk.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Deziel, N. C., Ward, M. H., Bell, E. M., Whitehead, T. P., Gunier, R. B., Friesen, M. C., Nuckols, J. R.","Temporal variability of pesticide concentrations in homes and implications for attenuation bias in epidemiologic studies","","121(5):565-571","e0b97c01-7139-4695-b1ef-4cbf15e204b9","","Background: Residential pesticide exposure has been linked to adverse health outcomes in adults and children. High-quality exposure estimates are critical for confirming these associations. Past epidemiologic studies have used one measurement of pesticide concentrations in carpet dust to characterize an individual's average long-term exposure. If concentrations vary over time, this approach could substantially misclassify exposure and attenuate risk estimates. Objectives: We assessed the repeatability of pesticide concentrations in carpet dust samples and the potential attenuation bias in epidemiologic studies relying on one sample. Methods: We collected repeated carpet dust samples (median = 3; range, 1-7) from 21 homes in Fresno County, California, during 2003-2005. Dust was analyzed for 13 pesticides using gas chromatography-mass spectrometry. We used mixed-effects models to estimate between- and within-home variance. For each pesticide, we computed intraclass correlation coefficients (ICCs) and the estimated attenuation of regression coefficients in a hypothetical case-control study collecting a single dust sample. Results: The median ICC was 0.73 (range, 0.37-0.95), demonstrating higher between-home than within-home

variability for most pesticides. The expected magnitude of attenuation bias associated with using a single dust sample was estimated to be â‰¤ 30% for 7 of the 13 compounds evaluated. Conclusions: For several pesticides studied, use of one dust sample to represent an exposure period of approximately 2 years would not be expected to substantially attenuate odds ratios. Further study is needed to determine if our findings hold for longer exposure periods and for other pesticides.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2008","Zhu, H., Rusyn, I., Richard, A., Tropsha, A.","Use of cell viability assay date improves the prediction accuracy of conventional quantitative structure-activity relationships models of animal carcinogenicity","","116(4):506-513","a28be0cf-1615-4192-bd41-5ecc8a987a34","","Background: To develop efficient approaches for rapid evaluation of chemical toxicity and human health risk of environmental compounds, the National Toxicology Program (NTP) in collaboration with the National Center for Chemical Genomics has initiated a project on high-throughput sceening (HTS) of environmental chemicals. The first HTS results for a set of 1,408 compounds tested for their effects on cell viability in six: different cell lines have recently become available via PubChem. Objective: We have explored these data in terms of their utility for predicting adverse health effects of the environmental agents. Methods and Results: Initially the classification k nearest neighbor (kNN) quantitative structure-activity relationship (QSAR) modeling method was applied to the HTS data only, for a cutated data set of 384 compounds. The resulting models had prediction accuracies for training, test. (containing 275 compounds together), and external validation (109 compounds) sets as high as 89%, 71%, and 74%, respectively. We then asked if HTS results could be of value in predicting rodent carcinogenicity. We identified 383 compounds for which data were available from both the Berkeley Carcinogenic Potency Database and NTP-HTS studies. We found that compounds classified by HTS as ""actives"" in at least one cell line were likely to be rodent carcinogens (sensitivity 77%); however, HTS ""inactives"" were far less informative (specificity 46%). Using chemical descriptors only, kNN QSAR modeling resulted in 62.3% prediction accuracy for rodent carcinogenicity applied to this data set. Importantly, the prediction accuracy of the model was significantly improved (72.7%) when chemical descriptors were augmented by HTS data, which were regarded as biological descriptors. Conclusions: Our studies suggest that combining NTP-HTS profiles with conventional chemical descriptors could considerably improve the predictive power of computational approaches in toxicology.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2015","Akoto, O., Gavor, S., Appah, M. K., Apau, J.","Estimation of human health risk associated with the consumption of pesticide-contaminated vegetables from Kumasi, Ghana","","187(5)","82b4dd2a-8ff7-4b35-818e-048f78a645d9","","Analysis of pesticides consisting of 12 organophosphates (OPs), 10 organochlorines (OCs), and 6 pyrethroids in vegetables from Kumasi was conducted. Vegetable samples comprising 20 each of eggplants, okra, and tomatoes were analyzed. The method involves solvent extraction of pesticide residues followed by cleanup using silica gel. Residue analysis was carried out using a GC equipped with pulsed flame photometric detector for OP residues and electron capture detector for OC and pyrethroid residues. The results revealed that methamidophos exceeded the maximum residue limits (MRLs) in all vegetable commodities. Levels of malathion and dimethoate also exceeded the MRLs in eggplant and tomato samples. Endrin, Î±-endosulfan, Î³-

hexachlorocyclohexane (HCH), Î³-chlordane, and heptachlor exceeded their MRLs in okra samples whereas methoxychlor, allethrin, and deltamethrin exceeded in eggplant samples. Health risk estimation revealed that dimethoate in tomato and endrin, heptachlor, Î³-HCH, and Î³-chlordane in okra could not pose potential toxicity to the consumer. The combined risk index showed no health risk to consumers due to intake of pyrethroid OC and OP residue on these vegetables. The overall risk index for combined pesticides due to consumption of all the vegetables was higher than 1, which signifies potential health risk to consumers. OPs were the major risk contributor for both eggplant and tomatoes which accounted for 87.78 and 95.84Â %, respectively, of the combined risk of pesticides in the vegetables. However, OC with 97.94Â % of the combined risk index was the major risk contributor for the okra. The carcinogenic risk of the OCs in okra was of no concern since their carcinogenic rates were below the acceptable risk level.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2009","Rudzok, S., SchmÃ¼cking, E., Graebsch, C., Herbarth, O., Bauer, M.","The inducibility of human cytochrome P450 1A by environmental-relevant xenobiotics in the human hepatoma derived cell line HepG2","","28(3):370-378","ab279ccc-a9ae-48ca-92a8-b60d17ef80c4","","Overexpression of the CYP1 family, independent of gender, is focal to the evaluation of the risk of human cancer. We have analysed the ability of 17 anthropogenic environmental xenobiotics widely used in Europe within households and agriculture to induce the human cytochrome P450 1A (CYP1A) in the human hepatoma derived cell line HepG2. The xenobiotics were potent to concomitantly induce both CYP1A mRNA and CYP1A activity in a dose-response relationship. Exceptions were shown by the organophosphate insecticide chlorpyrifos and the imidazole fungicide prochloraz in high concentrations which were capable of both inhibiting the basal or abolishing the initially induced CYP1A activity, respectively. A CYP1A induction has been shown for the first time by the aromatic xenobiotics irgasan, permethrin and azoxystrobin, the nonaromatic tributyltinoxide and for humans by the piperonylbutoxide. The xenobiotics additionally differed by their induced CYP1A isoenzyme pattern. A pronounced CYP1A1 and CYP1A2 mRNA induction was given by the phenyl urea herbicide diuron and benzodiazole insecticide piperonylbutoxide, respectively. In conclusion, out of the environmental xenobiotics, we described new members of human CYP1A inducers which extend chemical structures of biotransformation activators. Â© 2009 Elsevier B.V. All rights reserved.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2008","Mink, P. J., Adami, H. O., Trichopoulos, D., Britton, N. L., Mandel, J. S.","Pesticides and prostate cancer: A review of epidemiologic studies with specific agricultural exposure information","","17(2):97-110","07f829f6-9a8b-41e7-a131-cd029bb8b8d6","","Prostate cancer is the most commonly diagnosed cancer in US men, and the second most commonly diagnosed cancer among men worldwide. Although pesticides have been implicated in studies of prostate cancer among farmers, meta-analyses have found heterogeneity across studies, and a number of exposures and lifestyle factors may be unique to farmers. The purpose of this paper is to review the epidemiologic literature to evaluate the hypothesis that agricultural exposure to pesticides is causally associated with prostate cancer risk. We analyzed the eight cohort studies and five case-control studies that quantified and/or evaluated agricultural exposure to particular pesticide classes or chemicals. Despite sporadic positive findings, these studies did not show consistently increased risks to support a causal association between agricultural

pesticide use and prostate cancer. Studies using an 'external' comparison group must be interpreted in the context of confounding by differences in prostate-specific antigen screening intensity. Furthermore, most studies did not adjust for potential confounders other than age and time period. It is clearly not possible to exonerate any particular pesticide as a putative cause of prostate cancer - to do so would require an inverse empirical association with an upper confidence limit below the null value. Existing evidence does not point to any pesticide as satisfying widely used guidelines for establishing causation: a strong, exposure-dependent and demonstrably unconfounded, unbiased association, documented in several studies. Â© 2008 Lippincott Williams & Wilkins, Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Proskocil, B., Lein, P., Jacoby, D., Fyer, A.","Organophosphorus pesticides directly simulate macrophages to increase expression of growth factors and cytokines","","44","f85c42ce-ddb8-416f-bfb2-1e13b4b6f304","","A single s.c. injection of the organophosphorus pesticides (OPs) parathion, chlorpyrifos, or diazinon causes airway hyperreactivity and neuronal M2 muscarinic receptor dysfunction in guinea pigs 24 hr later. OP-induced airway hyperreactivity is dependent on tumor necrosis factor Î± (TNFÎ±) but independent of interleukin-1Î² (IL-1Î²) or inhibition of acetylcholinesterase (AChE) (Proskocil BJ et al., Am J Physiol Lung Cell Mol Physiol. 2013; 304:L519-29). We tested whether OPs and their oxon metabolites directly stimulate human macrophages to increase expression of factors that modulate neuronal M2 receptors. THP1 cells, a human monocyte cell line differentiated into macrophage-like cells, were treated with 1-100 Î¼M parathion, chlorpyrifos, or diazinon or 1-100 nM paraoxon, chlorpyrifos oxon, or diazoxon for 24 hr. mRNA was measured by real-time PCR and released proteins were analyzed by ELISA. None of the OPs or oxons affected cell viability. Parathion, chlorpyrifos, and diazinon increased mRNA expression of TNFÎ±, IL-1Î², platelet derived growth factor (PDGF), and transforming growth factor Î² (TGFÎ²) in a concentration-dependent manner. TNFÎ± protein was significantly increased at 100 Î¼M, however IL-1Î² and PDGF proteins were not increased and fibroblast growth factor (FGF) and TGFÎ² proteins were undetectable. No oxon metabolite increased mRNA or protein levels of these factors. Thus, the parent compounds, but not the oxon metabolites, directly stimulate THP-1 TNFÎ± protein and RNA expression of factors known to modulate M2 muscarinic receptors. These data correlate with our in vivo data demonstrating that OP-induced airway hyperreactivity occurs independent of AChE inhibition.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","El-Baz, M. A. H., El-Deek, S. E. M., Sayed, A. A., Amin, A. F.","In utero pesticides exposure and generation of acute myloid leukemia associated translocation (8;21)","","282:164-165","4a8f4945-c5e1-4fa5-8200-7ff3091f76ed","","Background: Although the etiology of childhood acute myeloid leukemia (AML) is not known, environmental and genetic contribution were reported. The aim of this study was to detect the relationship between in utero-exposure to pesticides and development of acute myeloid leukemia (AML) associated translocation (8;21). Subject and methods: Cord blood and fetal meconium were collected from 190 subjects. Four Pesticides (DDT, Lindane, Diazinon, and Malathion) were detected in meconium by gas chromatography and mass-spectrometry (GC-MS). AML translocation (8;21) was detected by RT-PCR on RNA extracted from cord blood. Results: Thirty eight out of 190 (20%) of the cord blood samples were positive for the AML1-ETO translocation. The mean levels of the 4 tested pesticides were higher in meconium of the AML-ETO translocation carriers; P value is < 0.001 for DDT, and Malathion, 0.004 for Diazinone,

and 0.042 for Lindane. Rural residents showed higher frequency of translocation detection than urban residents (P value = 0.007), they also expressed higher values of pesticides; P values are 0.04, 0.02, 0.04, and 0.01 for DDT, Lindane, Malathion, and Diazinon respectively. Maternal age, gestational age, birth weight and working status of the mothers showed no impact on the rate of translocation detection or pesticides levels. Conclusion: Pesticides exposure is potentially related to the occurrence of AML (8;21)translocation in cord blood of the apparently healthy newborn. Being rural resident seems to increase the possibility of exposure to pesticides; it subsequently imparts a higher risk for carrying such leukemia translocation. Strict regulation for pesticides uses is indicated.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2007","Giron-Perez, M. I., Santerre, A., Gonzalez-Jaime, F., Casas-Solis, J., Hernandez-Coronado, M., Peregrina-Sandoval, J., Takemura, A., Zaitseva, G.","Immunotoxicity and hepatic function evaluation in Nile tilapia (Oreochromis niloticus) exposed to diazinon","Fish & shellfish immunology","23(4):760-9","f273d3e4-838a-488f-87d7-0eee6759455a","","The LC(50) of the organophosphorus pesticides (OPs) diazinon to Nile tilapia (Oreochromis niloticus) was determined, thereafter, hepatic activity, phagocytic index, percentages of active cells, relative spleen weight, total IgM concentration and lymphoproliferation rates were compared between diazinon exposed groups (LC(50) and (1/2)LC(50)) and non-exposed control group. Experimental data show that diazinon is highly toxic for juvenile Nile tilapia (LC(50)=7.830 ppm) and presents immunotoxic properties which affect both the innate and cellular adaptive immune responses of this fish, as revealed by the fact that splenocyte proliferation and phagocytic indices were significantly decreased after acute exposure to the pesticide. However, the hepatic biochemical parameters and the total circulating IgM concentrations were not affected in this experimental model.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2008","Giron-Perez, M. I., Zaitseva, G., Casas-Solis, J., Santerre, A.","Effects of diazinon and diazoxon on the lymphoproliferation rate of splenocytes from Nile tilapia (Oreochromis niloticus): the immunosuppresive effect could involve an increase in acetylcholine levels","Fish & shellfish immunology","25(5):517-21","27d40a05-ea48-43dc-94da-3e4d4c93d320","","The lymphoproliferation rate of spleen cells from Nile tilapia (Oreochromis niloticus) exposed to the organophosphorus pesticide diazinon, to its metabolite diazoxon and to the neurotransmitter acetylcholine, was evaluated in order to explore the immunotoxic mechanism of action of this widely used insecticide. The lymphoproliferative response of spleen cells to mitogenic stimulus was not affected by either diazinon or diazoxon, indicating that these xenobiotic substances do not have direct immunotoxic properties. Conversely, ex vivo assays showed that spleen from fish exposed to diazinon presented a lower acetylcholinesterase activity and a higher acetylcholine concentration than non-exposed controls. Lymphoproliferation assays also indicated that pre-exposure to acetylcholine depleted the proliferative function of spleen cells. Thus the combined information from in vitro and ex vivo experiments suggest that the immunotoxic properties of diazinon in Nile tilapia are indirect and could involve the cholinergic system of lymphocytes.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2014","Alavizadeh, S. H., Hosseinzadeh, H.","Bioactivity assessment and toxicity of crocin: A comprehensive review","","64:65-80","3553f2ae-d8f4-41be-b4e2-4d4aed52eb8d","","Since ancient times, saffron, the dried stigma of the plant Crocus sativus L. has been extensively used as a spice and food

colorant; in folk medicine it has been reputed to be efficacious for the alleviation and treatment of ailments. In addition to the three founded major constituents including crocin, picrocrocin and safranal, presence of carotenoids, carbohydrates, proteins, anthocyanins, vitamins and minerals provide valuable insights into the health benefits and nutritional value of saffron. Of the carotenoids present in saffron, highly water-soluble crocin (mono and diglycosyl esters of a polyene dicarboxylic acid, named crocetin) is responsible for the majority of its color, and appears to possess various health-promoting properties, as an antioxidant, antitumor, memory enhancer, antidepressant, anxiolytic and aphrodisiac. It is also worth noting that the crocin principle of saffron exhibited high efficacy along with no major toxicity in experimental models. We would be remiss to not consider the great potential of saffron and crocin, which benefits the cuisine and health of human life throughout the world. The present study provides a comprehensive and updated report of empirical investigations on bioactivities and biological characteristics of crocin. Â© 2013 Elsevier Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Hariri, A. T., Moallem, S. A., Mahmoudi, M., Memar, B., Hosseinzadeh, H.","Sub-acute effects of diazinon on biochemical indices and specific biomarkers in rats: Protective effects of crocin and safranal","","48(10):2803-2808","63de17c7-a43f-47e4-a36f-cd37bc2c94db","","In this study, the effects of crocin and safranal were studied against sub-acute toxicity of diazinon (DZN) on specific biomarkers, biochemical indices and enzymes levels in rats. Vitamin E (200IU/kg), safranal at doses 0.025, 0.05 and 0.1ml/kg and crocin at doses 50, 100 and 200mg/kg were injected intraperitoneally three times per week alone or with DZN (20mg/kg/day, orally) for 4weeks. The parameters were evaluated at the end of 4weeks. Diazinon did not change serum urea, creatinine, cholesterol, triglyceride, total and direct bilirubin levels. Total protein and albumin concentrations were decreased by diazinon. Crocin, safranal and vitamin E prevented the effect of diazinon on some biochemical indices and enzymes levels. The levels of serum TNF-Î±, direct 8-iso-prostaglandin F2Î± and soluble protein-100 Î² (S100Î²) were increased significantly by diazinon. The augmentation of direct 8-iso-prostaglandin F2Î± and S100Î² levels by diazinon was significantly decreased by crocin, safranal and vitamin E. TNF-Î± level was significantly decreased in diazinon plus crocin 50 and 100mg/kg treated groups compared to the diazinon group. This study showed that vitamin E, safranal and crocin could prevent diazinon induced enzymes elevation and augmentation of some specific biomarkers. Â© 2010 Elsevier Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Perez-Carreon, J. I., Dargent, C., Merhi, M., Fattel-Fazenda, S., Arce-Popoca, E., Villa-TreviÃ±o, S., Rouimi, P.","Tumor promoting and co-carcinogenic effects in medium-term rat hepatocarcinogenesis are not modified by co-administration of 12 pesticides in mixture at acceptable daily intake","","47(3):540-546","45b44f8a-eac3-469c-ab9b-8a38e9ade943","","The purpose of this investigation was to evaluate the possible influence of a mixture of pesticides on medium-term carcinogenesis using improved hepatocarcinogenesis protocols. We performed a 12 commercially available pesticides combination with alachlor, atrazine, carbofuran, chlorpyrifos, diazinon, dicofol, endosulfan, iprodione, mancozeb, maneb, procymidone and rotenone. The mixture was given at 1-fold and 10-fold the acceptable daily intake (ADI) level in a set of Solt-Farber-derived protocols involving diethylnitrosamine, 2-acetylaminofluorene treatments and a partial hepatectomy. Co-carcinogenic effect and promoting activity were evaluated using

Î³-glutamyl transpeptidase (GGT) positive altered hepatocyte foci, as well, protein and mRNA levels of glutathione S-transferase P (GSTP) in liver extracts as molecular biomarkers of carcinogenic effects. The pesticide treatments when compared to vehicle treatments always produced the same number of hepatocyte lesions and an equal GSTP expression on liver extracts independently of carcinogenic-protocol utilized. On this base, we concluded that the pesticide mixture evaluated in this report does not have tumor promoting activity or co-carcinogenic effect in the rat medium-term liver carcinogenesis. Altogether these data contribute to the confidence that the ADI represents a safe intake level to mixture of pesticides at dietary exposure. Â© 2008 Elsevier Ltd. All rights reserved.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Deme, P., Azmeera, T., Prabhavathi Devi, B. L., Jonnalagadda, P. R., Prasad, R. B., Vijaya Sarathi, U. V.","An improved dispersive solid-phase extraction clean-up method for the gas chromatography-negative chemical ionisation tandem mass spectrometric determination of multiclass pesticide residues in edible oils","Food chemistry","142:144-51","88b1d5a5-d323-4fa4-8506-d92f7bae8209","","An improved sample preparation using dispersive solid-phase extraction clean-up was proposed for the trace level determination of 35 multiclass pesticide residues (organochlorine, organophosphorus and synthetic pyrethroids) in edible oils. Quantification of the analytes was carried out by gas chromatography-mass spectrometry in negative chemical ionisation mode (GC-NCI-MS/MS). The limit of detection and limit of quantification of residues were in the range of 0.01-1ng/g and 0.05-2ng/g, respectively. The analytes showed recoveries between 62% and 110%, and the matrix effect was observed to be less than 25% for most of the pesticides. Crude edible oil samples showed endosulfan isomers, p,p'-DDD, alpha-cypermethrin, chlorpyrifos, and diazinon residues in the range of 0.56-2.14ng/g. However, no pesticide residues in the detection range of the method were observed in refined oils.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Falugi, C., Aluigi, M. G.","Early appearance and possible functions of non-neuromuscular cholinesterase activities","","(APRIL):1-19","65150599-35cf-4f98-bcc9-801fbb2267a4","","The biological function of the cholinesterase (ChE) enzymes has been studied since the beginning of the 20th century. Acetylcholinesterase plays a key role in the modulation of neuromuscular impulse transmission in vertebrates, while in invertebrates pseudo cholinesterases are preeminently represented. During the last forty years, awareness of the role of ChEs role in regulating non-neuromuscular cell-to-cell interactions has been increasing such as the ones occurring during gamete interaction and embryonic development. Moreover, ChE activities are responsible for other relevant biological events, including regulation of the balance between cell proliferation and cell death, as well as the modulation of cell adhesion and cell migration. Understanding the mechanisms of the regulation of these events can help us foresee the possible impact of neurotoxic substances on the environmental and human health.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Mankame, T., Hokanson, R., Fudge, R., Chowdhary, R., Busbee, D.","Alteration of gene expression in human cells treated with the agricultural chemical diazinon: possible interaction in fetal development","Human & experimental toxicology","25(5):225-33","019e3176-87d6-4bc7-a84f-e7c69a138d22","","Agricultural chemicals frequently alter human health or development, typically because they have endocrine agonist or antagonist activities and alter

hormone-regulation of gene expression. The insecticide, diazinon, was evaluated for gene expression disrupting activity using MCF-7 cells, an estrogen-dependent human cell line, to examine the capacity of the insecticide to disrupt gene expression essential for morphological development, immune system development or function, and/or central nervous system development and function. MCF-7 cells were treated with 30, 50 or 67 ppm diazinon, and gene expression was measured in treated cells compared to expression in untreated or estrogen-treated cells. DNA microarray analysis of diazinon-treated cells showed significant up- or down-regulation of a large number of genes compared to untreated cells. Of the 600 human genes on the Phase 1 chip utilized for these studies, two specific genes--calreticulin and TGF-beta3--were selected for corroboration using quantitative real time PCR (qrtPCR). qrtPCR, completed to assess gene expression levels for calreticulin and TGFbeta3, confirmed results showing significant up-regulation of these two genes obtained from the microarray data. These studies were designed to provide baseline data on the gene expression-altering capacity of a specific chemical, diazinon, and allow a partial assessment of the potentially deleterious effects associated with exposure of human cells to this chemical. Currently, it is not known whether results from cells in vitro can be extrapolated to human health consequences of chemical exposure.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Karami-Mohajeri, S., Abdollahi, M.","Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: A systematic review","","30(9):1119-1140","6447ff4c-e793-4a80-8838-741ea76ab81e","","Pesticides, including organophosphate (OP), organochlorine (OC), and carbamate (CB) compounds, are widely used in agricultural and indoor purposes. OP and CB act as acetyl cholinesterase (AChE) inhibitors that affect lots of organs such as peripheral and central nervous systems, muscles, liver, pancreas, and brain, whereas OC are neurotoxic involved in alteration of ion channels. There are several reports about metabolic disorders, hyperglycemia, and also oxidative stress in acute and chronic exposures to pesticides that are linked with diabetes and other metabolic disorders. In this respect, there are several in vitro and in vivo but few clinical studies about mechanism underlying these effects. Bibliographic databases were searched for the years 1963-2010 and resulted in 1652 articles. After elimination of duplicates or irrelevant papers, 204 papers were included and reviewed. Results indicated that OP and CB impair the enzymatic pathways involved in metabolism of carbohydrates, fats and protein within cytoplasm, mitochondria, and proxisomes. It is believed that OP and CB show this effect through inhibition of AChE or affecting target organs directly. OC mostly affect lipid metabolism in the adipose tissues and change glucose pathway in other cells. As a shared mechanism, all OP, CB and OC induce cellular oxidative stress via affecting mitochondrial function and therefore disrupt neuronal and hormonal status of the body. Establishing proper epidemiological studies to explore exact relationships between exposure levels to these pesticides and rate of resulted metabolic disorders in human will be helpful. Â© 2011 SAGE Publications.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Mankame, T., Hokanson, R., Fudge, R., Chowdhary, R., Busbee, D.","Altered gene expression in human cells treated with the insecticide diazinon: Correlation with decreased DNA excision repair capacity","","25(2):57-65","17ba2fad-338f-4223-8c02-d378e6286383","","Many industrial and agricultural chemicals have steroid hormone agonist or antagonist activities and disrupt hormone-regulated gene expression. The widely-used agricultural insecticide,

diazinon, was evaluated using MCF-7 cells - a breast cancer-derived, estrogen-dependent, human cell line - to examine the capacity of this chemical to alter steroid hormone-regulated gene expression. MCF-7 cells were treated with 30, 50, or 67 ppm of diazinon, and gene expression in treated cells was measured as mRNA levels in the cells compared to mRNA levels in untreated or estrogen-treated cells. DNA microarray analysis showed significant up- or down-regulation of a number of genes in treated cells compared to untreated cells. Of the 600 human genes on the chip utilized, specific genes with related functions were selected for additional consideration. Real time quantitative PCR (qrtPCR) completed to corroborate mRNA levels as a measure of specific gene expression, confirmed results obtained from analysis of the microarray data. The data show that ERCC5, encoding Xeroderma pigmentosum protein G (XPG), essential for DNA excision repair, and ribonucleotide reductase subunit M1 (RNRM1), encoding a gene necessary for providing the nucleotides needed for DNA repair, were down-regulated in cells treated with diazinon. These studies were designed to provide base-line data on the gene expression-altering capacity of a specific agricultural chemical, diazinon, and allow assessment of some of the potentially deleterious effects associated with exposure of human cells to diazinon. Â© 2006 Edward Arnold (Publishers) Ltd.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2006","Younglai, E. V., Wu, Y. J., Foster, W. G.","Do insecticides have adverse effects on reproduction?","","6(1):45-56","3a0d40b8-cc81-489d-9945-95f35765597b","","In recent years considerable attention has been focused on the adverse effects of environmental toxicants on human reproductive processes. A major class of environmental toxicants is the pesticides which include insecticides, herbicides, fungicides, molluscicides, rodenticides and nematocides. Although some pesticides are no longer used, their metabolites persist for many years and are ubiquitous through long range transport. In this review we will examine the role of insecticides in adverse reproductive outcomes and their mechanisms of action. No attempt is made to link exposure to insecticides and carcinogenesis, immune response, congenital anomalies or other effects. The three groups of insecticides - carbamates, organochlorines, and organophosphates will be discussed in detail. Evidence for and against adverse effects of insecticides as well as the emerging area of interest on nongenomic effects will be covered. Â© 2006 Bentham Science Publishers Ltd.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2005","Kojima, M., Fukunaga, K., Sasaki, M., Nakamura, M., Tsuji, M., Nishiyama, T.","Evaluation of estrogenic activities of pesticides using an in vitro reporter gene assay","International journal of environmental health research","15(4):271-80","2f1a5ed1-6dcd-4522-9dcf-2b2222c03d29","","The estrogenic activities of 32 pesticides in agricultural products were evaluated using the E-CALUX assay system developed by Xenobiotic Detection Systems Inc (North Carolina, USA). This system utilizes human ovarian carcinoma cells (BG1) stably transfected with an estrogen-responsive luciferase reporter gene plasmid. It was found that tolclofos-methyl, prothiofos, diazinon, Thiabenclazole (TBZ) and pyriproxyfen had estrogenic activity. Several pesticides are often present in agricultural products. Therefore the estrogenicity of the mixtures of two kinds of pesticides was evaluated. The activity of diazinon/tolclofos-methyl, pyriproxyfen/prothiofos and TBZ/o-phenylphenol (OPP) was increased up to 1.2-5.3 fold. On the other hand, chlorfluazuron, imazalil and chlorfenapyr had anti-estrogenic activity. Further, to evaluate the change in the estrogenic activity of pesticide

metabolites, an experimental system was established using a rat S9 mixture. Metabolites of permethrin and OPP had no estrogenic activity, but they had weak activity after the metabolism. On the other hand, the metabolites of TBZ exhibited less estrogenic activity than the original compounds.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Manabe, M., Kanda, S., Fukunaga, K., Tsubura, A., Nishiyama, T.","Evaluation of the estrogenic activities of some pesticides and their combinations using MtT/Se cell proliferation assay","International journal of hygiene and environmental health","209(5):413-21","7585a73d-5271-4fec-8d2e-dc7d5f61837b","","A number of pesticides are used in agricultural production with some having estrogenic activities, such as endocrine-disrupting chemicals that may affect wildlife and humans. This study aimed to detect the estrogenic effects of some mixed agricultural chemicals in agricultural production. The assay to measure estrogenic activity was evaluated by the cell proliferative activity of MtT/Se cells, which respond well to estrogen. To evaluate MtT/Se cells we went down to the molecular level of estrogen receptor (ER)-alpha and ER-beta expression. The proportion of ER-alpha to ER-beta was 3.55:1, as determined by semi-quantitative real-time PCR. These results showed that ER-alpha was dominant in MtT/Se cells on the transcriptional level, therefore implying that the estrogenic activity detected by these cells may be mainly mediated by ER-alpha. It was found that diazinon, tolclofos-methyl, pyriproxyfen, prothiofos and thiabendazole had estrogenic activity. Several pesticides are often present in agricultural products. Therefore, we evaluated the estrogenic activity of a mixture of two pesticides. The REC(10) levels of prothiofos/pyriproxyfen and thiabendazole/orthophenylphenol were increased up to 10-fold. We concluded that those two pesticide combinations showed a significantly higher estrogenic effect in comparison to the results of the respective pesticides when tested individually.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Sadri, S., Bahrami, F., Khazaei, M., Hashemi, M., Asgari, A.","Cannabinoid receptor agonist WIN-55,212-2 protects differentiated PC12 cells from organophosphorus- induced apoptosis","International journal of toxicology","29(2):201-8","79382de3-fa48-427a-8fce-9e21865aada2","","Cannabinoid neuroprotection is usually greater in vivo than in neuronal cell culture systems. To the authors' knowledge, a good in vitro culture model for the neuroprotective effects of cannabinoids does not exist. Therefore, a 3-dimensional (3D) culture system was developed to investigate the neuroprotective effects of the cannabinoid receptor agonist WIN-55,212-2 on apoptosis of differentiated PC12 cells, caused by the organophosphorus compounds paraoxon and diazinon. Cells pretreated with WIN-55,212-2 were exposed to a proapoptotic concentration of paraoxon and diazinon. TUNEL was used to detect apoptosis, and neurite length was assessed by morphometry. Both paraoxon and diazinon induced apoptosis, although the latter was more potent. WIN-55,212-2 also protected cells from neurite retraction and DNA fragmentation induced by the OPs. The results suggest that WIN-55,212-2 protects PC12 cells cultured under 3D conditions from organophosphorus-induced apoptosis. This 3D culture system may prove to be a useful tool for investigating the neuroprotective effects of cannabinoids.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Barrett, K., Jaward, F. M.","A review of endosulfan, dichlorvos, diazinon, and diuron - Pesticides used in Jamaica","","22(6):481-499","3d656718-f40f-470d-bbb1-edfce42647e6","","The global agricultural sector is the primary user of pesticides, consuming more than three

billion kilograms of pesticides annually. Although pesticides are beneficial in controlling the proliferation of pests, they have been associated with adverse human and ecological impacts. Approximately 87% of the annually imported pesticides in Jamaica are applied within agricultural or household settings. However, in Jamaica, the potential impact on humans, their property, and the environment is unknown, as the fate of many of the locally applied pesticides has not been established. This review discusses four pesticides extensively applied in agricultural practices in Jamaica - endosulfan, diazinon, diuron, and dichlorvos. The information presented is essential for the development of fate and transport models of these chemicals. Consequently, health and ecological impact assessments may be conducted from the generated models. Â© 2012 Copyright Taylor and Francis Group, LLC.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Schinasi, L., Leon, M. E.","Non-hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: A systematic review and meta-analysis","","11(4):4449-4527","9e211ce8-800a-4862-b8a9-8898a20c7b9f","","This paper describes results from a systematic review and a series of meta-analyses of nearly three decades worth of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to agricultural pesticide active ingredients and chemical groups. Estimates of associations of NHL with 21 pesticide chemical groups and 80 active ingredients were extracted from 44 papers, all of which reported results from analyses of studies conducted in high-income countries. Random effects meta-analyses showed that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL. In a handful of papers, associations between pesticides and NHL subtypes were reported; B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure. Despite compelling evidence that NHL is associated with certain chemicals, this review indicates the need for investigations of a larger variety of pesticides in more geographic areas, especially in low- and middle-income countries, which, despite producing a large portion of the world's agriculture, were missing in the literature that were reviewed. Â© 2014 by the authors; licensee MDPI, Basel, Switzerland.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Malathi, M., Ramya Devi, D., Vedha Hari, B. N.","Crocus sativus Linn - A potential source for diverse therapeutic applications","","26(2):299-305","5d3e8831-eca0-4de8-8e21-056257ee84f5","","The dried red stigma of Crocus sativus L. belonging to Iridaceae family is a variety of spice commercially named as Saffron. It consists of more than 150 volatile compounds chiefly the terpenes and their esters and it belongs to native of Greece and South west Asia. Saffron has the medicinally important activities such as anticancer, anti-inflammatory, antitussive, antioxidant, anxiolytic, aphrodisiac, antinociceptive, anticonvulsant, antihypertensive, antidepressant, antigenototoxic and relaxant activity. Literatures suggest extraction method like hydro distillation using cold, hot water and ethanol for collecting the active components of the leaves and flowers of Crocus sativus L. (saffron). The collected essential oil and other chemical constituents were investigated by the researchers by using GC/MS technique. The objective of this review is to highlight the salient features, biological activities and extraction methods for the active components of the plant.","","","RefMan","","","","","","","","","","

"Unknown","Unknown","Unknown","Unknown","","","2013","Rezaee, R., Hosseinzadeh, H.","Safranal: From an aromatic natural product to a rewarding pharmacological agent","","16(1):12-26","cb91be93-1ac2-4614-8041-a1e2aa508f2a","","Safranal, the main component of Crocus sativus essential oil, is thought to be the main cause of saffron unique odor. It is now about eighty years that this compound has been discovered and since then different scientific experiments have been done investigating its biological-pharmacological activities. Safranal effects in CNS have been more attractive to scientists and an escalating number of papers have been published regarding its neuropsychological effects. These promising properties of safranal propose its presence as a therapeutic agent in future, although there is a great need for further clinical trials and toxicological studies. In this review article, according to Scopus Â®, Thomson Reuters Web of KnowledgeÂ®, Scientific Information Database (SID) Â® and Pubmed Â® all papers published until July 2012 were thoroughly discussed and a brief note of each study was prepared.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2007","Bailey, R., Belzer, W.","Large volume cold on-column injection for gas chromatography-negative chemical ionization-mass spectrometry analysis of selected pesticides in air samples","Journal of agricultural and food chemistry","55(4):1150-5","315d8eaf-4f00-422a-8c03-763327087bc1","","A new gas chromatographic method is described for the analysis of fungicides captan, captafol, and folpet from organic extracts of air samples using large volume injection (LVI) via a cold on-column (COC) inlet coupled with gas chromatography-negative chemical ionization-mass spectrometry (GC-NCI-MS). Although standard split/splitless injection due to high injection port temperatures (>225 degrees C) have been shown to degrade these thermally labile fungicides, COC injection minimizes degradation. Insecticides such as chlorpyrifos and diazinon were also examined to show added selectivity. By using a solvent vapor exit with the COC inlet, injection volumes of 10-100 microL can be made to lower detection levels. GC-NCI-MS was compared to GC-electron impact ionization-mass spectrometry for each pesticide using LVI-COC injections and was found to be 2-80 times more sensitive, depending on the pesticide. Method detection limit (MDL) values with 100 microL injections were 2.5 microg L-1 for captan, folpet, and diazinon, 5.0 microg L-1 captafol, and 1.0 microg L-1 for chlorpyrifos, with the normal working range examined for sample analysis from MDL to 100 microg L-1. Detection of all pesticides except captafol, used only in the United States but not Canada, was demonstrated from air samples taken from Abbotsford, British Columbia, Canada.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2005","Tutudaki, M., Tsatsakis, A. M.","Pesticide hair analysis: development of a GC-NCI-MS method to assess chronic exposure to diazinon in rats","Journal of analytical toxicology","29(8):805-9","5b29c81d-827c-4cca-a850-cf71549eeec7","","The present study aimed to improve the gas chromatography-mass spectrometry (GC-MS) method, already developed in our laboratory, for trace analysis of diazinon in hair. Furthermore, it aimed to compare the disposition of the pesticide in the hair of two different animal species, one susceptible to diazinon toxicity and one resistant, under identical experimental conditions. Sprague Dawley rats were systemically exposed to two dose levels (6 mg/kg/day and 3 mg/kg/day) of the pesticide, through their drinking water, for a period of one and a half months. Hair samples from the back of the rats were removed before commencing the experiment and at the end of the dosing period. Diazinon was selectively

isolated from pulverized hair, sample or spiked, by stepwise consequent extractions with methanol and ethyl acetate and quantified by GC-negative chemical ionization-MS. It was found that the concentration of diazinon in the hair of exposed animals was dose dependent and was found to be 0.24 +/- 0.01 ng/mg (n = 5) and 0.53 +/- 0.05 ng/mg (n = 5) for the low and high dosage, respectively. The concentration in both dose groups was much higher than the corresponding rabbit hair (rabbits were exposed to the pesticide under similar experimental conditions) as previously reported. Our results strongly point to the possibility of using hair analysis for low-level exposure monitoring of diazinon.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Tacal, O., Lockridge, O.","Methamidophos, dichlorvos, O-methoate and diazinon pesticides used in Turkey make a covalent bond with butyrylcholinesterase detected by mass spectrometry","Journal of applied toxicology : JAT","30(5):469-75","adae0529-baa0-4531-b786-615db524ac23","","Organophosphorus pesticides used most commonly in Turkey include methamidophos, dichlorvos, O-methoate and diazinon. These toxic chemicals or their metabolites make a covalent bond with the active site serine of butyrylcholinesterase. Our goal was to identify the adducts that result from the reaction of human butyrylcholinesterase with these pesticides. Highly purified human butyrylcholinesterase was treated with a 20-fold molar excess of pesticide. The protein was denatured by boiling and digested with trypsin. MS and MSMS spectra of HPLC-purified peptides were acquired on a MALDI-TOF-TOF 4800 mass spectrometer. It was found that methamidophos added a mass of +93, consistent with addition of methoxy aminophosphate. A minor amount of adduct with an added mass of +109 was also found. Dichlorvos and O-methoate both made dimethoxyphosphate (+108) and monomethoxyphosphate adducts (+94). Diazinon gave a novel adduct with an added mass of +152 consistent with diethoxythiophosphate. Inhibition of enzyme activity in the presence of diazinon developed slowly (15 h), concomitant with isomerization of diazinon via a thiono-thiolo rearrangement. The isomer of diazinon yielded diethoxyphosphate and monoethoxyphosphate adducts with added masses of +136 and +108. MSMS spectra confirmed that each of the pesticides studied made a covalent bond with serine 198 of butyrylcholinesterase. These results can be used to identify the class of pesticides to which a patient was exposed.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1999","Fabrizi, L., Gemma, S., Testai, E., Vittozzi, L.","Identification of the cytochrome P450 isoenzymes involved in the metabolism of diazinon in the rat liver","Journal of biochemical and molecular toxicology","13(1):53-61","667c0157-8ada-4129-8fce-73a9eb7bf3ec","","The metabolism of diazinon, an organo-phosphorothionate pesticide, to diazoxon and pyrimidinol has been studied in incubations with hepatic microsomes from control Sprague-Dawley (SD) rats or SD rats treated with different P450-specific inducers (phenobarbital, dexamethasone, beta-napthoflavone, and pyrazole). Results obtained indicate an involvement of CYP2C11, CYP3A2, and CYP2B1/2, whereas CYP2E1 and CYP1A1 do not contribute to the pesticide oxidative metabolism. Indeed, diazinon was metabolized by microsomes from control rats; among the inducers, phenobarbital and dexamethasone only increased the production of either metabolites, although to different extents. The production of the two metabolites is self-limiting, due to P450 inactivation; therefore, the inhibition of CYP-specific monooxygenase activities after diazinon preincubation has been used to selectively identify the competent CYPs in diazinon metabolism. Results indicate that, after diazinon preincubation, CYP3A2-catalyzed reactions (2beta- and 6beta-testosterone

hydroxylation) are very efficiently inhibited; CYP2C11- and CYP2B1/2-catalyzed reactions (2alpha- and 16beta-testosterone hydroxylation, respectively) are weakly inhibited, while CYP2E1-, CYP2A1/2-, and CYP1A1/2-related activities were unaffected. Results obtained by using chemical inhibitors or antibodies selectively active against specific CYPs provide a direct evidence for the involvement of CYP2C11, CYP3A2, and CYP2B1/2, indicating that each of them contributed about 40-50% of the diazinon metabolism, in hepatic microsomes from untreated, phenobarbital-, and dexamethasone-treated rats, respectively. The higher diazoxon/pyrimidinol ratio observed after phenobarbital-treatment together with the significantly more effective inhibition toward diazoxon production exerted by metyrapone in microsomes from phenobarbital-treated rats supports the conclusion that CYP2B1/2 catalyze preferentially the production of diazoxon.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2006","Kochman, M., Gordin, A., Alon, T., Amirav, A.","Flow modulation comprehensive two-dimensional gas chromatography-mass spectrometry with a supersonic molecular beam","Journal of chromatography. A","1129(1):95-104","433fa747-c5e3-43be-8f6c-48837745f896","","A new approach of flow modulation comprehensive two-dimensional gas chromatography-mass spectrometry (GC x GC-MS) with supersonic molecular beam (SMB) and a quadrupole mass analyzer is presented. Flow modulation uniquely enables GC x GC-MS to be achieved even with the limited scan speed of quadrupole MS, and its 20 ml/min column flow rate is handled, splitless, by the SMB interface. Flow modulation GC x GC-SMB-MS shares all the major benefits of GC x GC and combines them with GC-MS including: (a) increased GC separation capability; (b) improved sensitivity via narrower GC peaks; (c) improved sensitivity through reduced matrix interference and chemical noise; (d) polarity and functional group sample information via the order of elution from the second polar column. In addition, GC x GC-SMB-MS is uniquely characterized by the features of GC-MS with SMB of enhanced and trustworthy molecular ion plus isotope abundance analysis (IAA) for improved sample identification and fast fly-through ion source response time. The combination of flow modulation GC x GC with GC-MS with SMB (supersonic GC-MS) was explored with complex matrices such as diesel fuel analysis and pesticide analysis in agricultural products.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2007","Mahler, B., Massei, N.","Anthropogenic contaminants as tracers in an urbanizing karst aquifer","Journal of contaminant hydrology","91(1-2):81-106","45309d65-eba9-4681-857c-bd57e5a76bee","","Karst aquifers are uniquely vulnerable to contamination. In the Barton Springs segment of the karstic Edwards aquifer (Texas, U.S.A.), urban contaminants such as pesticides and volatile organic compounds frequently are detected in spring base flow. To determine whether contaminant concentrations change in response to storms, and if they therefore might act as tracers of focused recharge, samples were collected from Barton Springs at closely spaced intervals following three storms. Two herbicides (atrazine and simazine), two insecticides (carbaryl and diazinon), and a solvent (tetrachloroethene) described breakthrough curves over a 1-week period following one or more storms. The breakthrough curves were decomposed into two to five log-normal subcurves, which were interpreted as representing pulses of contaminants moving through the aquifer. Each subcurve could be used in the same way as an artificial tracer to determine travel time to and recovery at the spring. The contaminants have several advantages over artificial tracers: they represent the actual compounds of interest, they are injected essentially simultaneously at several points,

and they are injected under those conditions when transport is of the most interest, i.e., following storms. The response of storm discharge, specific conductance, and contaminant loading at the spring depended on initial aquifer flow conditions, which varied from very low (spring discharge of 0.48 m3/s) to high (spring discharge of 2.7 m3/s): concentrations and recovery were the highest when initial aquifer flow conditions were low. This behavior provides information about aquifer structure and the influence of aquifer flow condition on transport properties.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Jayachandra, S., D'Souza, U. J.","Pre- and postnatal toxicity of diazinon induces disruption of spermatogenetic cell line evidenced by increased testicular marker enzymes activities in rat offspring","Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer","32(1):73-90","11ba708f-5409-441f-a39f-56189294eaca","","The objective of this study was to study the possible reproductive adverse effects of the diazinon on rat offspring exposed in utero and during lactation. Dams were gavaged daily (10, 15, and 30 mg/kg) before mating, during mating, and during pregnancy and lactation in separate groups. Reproductive outcome data of dams were examined. Body weight, testis weight, testicular marker enzyme activities (alkaline phosphatase, acid phosphatase, lactate dehydrogenase, and glucose-6-phosphate dehydrogenase), qualitative and quantitative testicular and epididymal histology, and immunohistochemisty for 3-beta-hydroxysteroid dehydrogenase (HSD) were examined in male offspring at puberty and adulthood. The 30-mg/kg dose induced significant adverse effects at both puberty and adulthood in offspring. At puberty the male offspring showed a decrease in testicular weight, degenerative changes, and 3-beta-HSD. Moreover, an increase in activity of alkaline and acid phosphatase also was observed. At adulthood, there was a decrease in testicular weight and 3-beta-HSD with an increase in the levels of testicular marker enzyme. There was evidence of some adverse reproductive effects in male offspring at the 15-mg/kg dose. Most of the adverse effects were irreversible and were evident at both puberty and adulthood in offspring, although a few parameters reverted back to the normal growth pattern. Hence, diazinon is a reproductive toxicant in male offspring, which caused significant damage to the testes when exposed during prenatal and postnatal life.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2003","Souza, D. A., Lancas, F. M.","Solventless sample preparation for pesticides analysis in environmental water samples using solid-phase microextraction-high resolution gas chromatography/mass spectrometry (SPME-HRGC/MS)","Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes","38(4):417-28","c3d9a3fd-8b90-481f-8b7b-89275672ac31","","Solid-phase micro-extraction (SPME) coupled on line with high resolution gas chromatography and mass spectrometric detection is described for the analysis of pesticides in environmental water samples. Experiments were performed in order to optimize the SPME extraction conditions for selected pesticides including tiomethon, trichorfon, dimethoate, diazinon, malathion, dicofol, methidathion, ethion, bromopropylate and pyrazophos from spiked water solutions. To enhance the SPME efficiency, experimental conditions including the fiber composition, stirring rate, temperature, adsorption time, desorption time and salt concentration were optimized. After validation, the SPME-GC/MS methodology was applied to real-world environmental water samples.","","","RefMan","","","","","","","","","","

"Unknown","Unknown","Unknown","Unknown","","","2004","Colt, J. S., Lubin, J., Camann, D., Davis, S., Cerhan, J., Severson, R. K., Cozen, W., Hartge, P.","Comparison of pesticide levels in carpet dust and self-reported pest treatment practices in four US sites","Journal of exposure analysis and environmental epidemiology","14(1):74-83","1744df90-abfd-4f21-a20e-f4253e92cd9d","","Epidemiologic studies have used both questionnaires and carpet dust sampling to assess residential exposure to pesticides. The consistency of the information provided by these two approaches has not been explored. In a population-based case-control study of non-Hodgkin's lymphoma, carpet dust samples were collected from the homes of 513 control subjects in Detroit, Iowa, Los Angeles, and Seattle. The samples were taken from used vacuum cleaner bags and analyzed for 30 pesticides. Interviewers queried subjects about the types of pests treated in their home using a detailed questionnaire accompanied by visual aids. Geographic variations in pesticide levels were generally consistent with geographic differences in pest treatment practices. Los Angeles residents reported the most treatment for crawling insects, fleas/ticks, and termites, and Los Angeles dust samples had the highest levels of propoxur, chlorpyrifos, diazinon, permethrin, and chlordane. Iowa had the most treatment for lawn/garden weeds, and also the highest levels of 2,4-dichlorophenoxyacetic acid and dicamba. Although Seattle had the highest proportion of subjects treating for lawn/garden insects, the lawn/garden insecticides were higher in other sites. Multivariate linear regression revealed several significant associations between the type of pest treated and dust levels of specific pesticides. The strongest associations were between termite treatment and chlordane, and flea/tick treatment and permethrin. Most of the significant associations were consistent with known uses of the pesticides; few expected associations were absent. The consistency between the questionnaire data and pesticide residues measured in dust lends credibility to both methods for assessing residential exposure to pesticides. The combined techniques appear promising for epidemiologic studies. Interviewing is the only way to assess pesticide exposures before current carpets were in place. Dust sampling provides an objective measure of specific compounds to which a person may have been exposed through personal use of a pesticide or by drift-in or track-in from outside, and avoids recall bias.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","1999","Gordon, S. M., Callahan, P. J., Nishioka, M. G., Brinkman, M. C., O'Rourke, M. K., Lebowitz, M. D., Moschandreas, D. J.","Residential environmental measurements in the national human exposure assessment survey (NHEXAS) pilot study in Arizona: preliminary results for pesticides and VOCs","Journal of exposure analysis and environmental epidemiology","9(5):456-70","278e021b-6da0-404b-bcb5-372c4774b779","","A major objective of the National Human Exposure Assessment Survey (NHEXAS) performed in Arizona was to conduct residential environmental and biomarker measurements of selected pesticides (chlorpyrifos, diazinon), volatile organic compounds (VOCs; benzene, toluene, trichloroethene, formaldehyde, 1,3-butadiene), and metals for total human exposure assessments. Both personal (e.g., blood, urine, dermal wipes, 24 h duplicate diet) and microenvironmental (e.g., indoor and outdoor air, house dust, foundation soil) samples were collected in each home in order to describe individual exposure via ingestion, inhalation, and dermal pathways, and to extrapolate trends to larger populations. This paper is a preliminary report of only the microenvironmental and dermal wipe data obtained for the target pesticides and VOCs, and provides comparisons with results from similar studies. Evaluations of total exposure from all sources and pathways will be addressed in future

papers. The pesticides and VOCs all showed log-normal distributions of concentrations in the Arizona population sampled, and in most cases were detected with sufficient frequency to allow unequivocal description of the concentration by media at the 90th, 75th, and 50th (median) percentiles. Those combinations of pollutant and media, in which a large fraction of the measurements were below the detection limit of the analysis method used, included trichloroethene, 1,3-butadiene, and formaldehyde in outdoor air; chlorpyrifos and diazinon in outdoor air; and diazinon in dermal and window sill wipes. In general, indoor air concentrations were higher than outdoor air concentrations for all VOCs and pesticides investigated, and VOC levels were in good agreement with levels reported in other studies. In addition, the agreement obtained between co-located VOC samplers indicated that the low-cost diffusional badges used to measure concentrations are probably adequate for use in future monitoring studies. For the pesticides, the median levels found in indoor samples agreed well with other studies, although the levels corresponding to the upper 0.1-1% of the population were considerably higher than levels reported elsewhere, with indoor air levels as high as 3.3 and 20.5 microg/m3 for chlorpyrifos and diazinon, respectively. These data showed excellent correlation (Pearson and Spearman correlation coefficients of 0.998 and 0.998, respectively) between chlorpyrifos in indoor air and in the corresponding dermal wipes, and relatively poor correlation between chlorpyrifos in dust (microg/g or microg/ml) and dermal wipes (Pearson=0.055 microg/g and 0.015 microg/m2; Spearman=0.644 microg/g and 0.578 microg/m2). These data suggest the importance of dermal penetration of semi-volatiles as a route of residential human exposure.","","","RefMan","","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2001","Wilson, N. K., Chuang, J. C., Lyu, C.","Levels of persistent organic pollutants in several child day care centers","Journal of exposure analysis and environmental epidemiology","11(6):449-58","6439c44f-c992-4162-bf8e-dce4868c1ab2","","The concentrations of a suite of persistent organic chemicals were measured in multiple media in 10 child day care centers located in central North Carolina. Five centers served mainly children from low-income families, as defined by the federal Women, Infants, and Children (WIC) assistance program, and five served mainly children from middle-income families. The targeted chemicals were chosen because of their probable carcinogenicity, acute or chronic toxicity, or hypothesized potential for endocrine system disruption. Targeted compounds included polycyclic aromatic hydrocarbons (PAHs), pentachloro- and nonyl-phenol, bisphenol-A, dibutyl and butylbenzyl phthalate, polychlorinated biphenyls (PCBs), organochlorine pesticides, the organophosphate pesticides diazinon and chlorpyrifos, and the herbicide 2,4-dichlorophenoxyacetic acid (2,4D). Sampled media were indoor and outdoor air, food and beverages, indoor dust, and outdoor play area soil. Concentrations of the targeted compounds were determined using a combination of extraction and analysis methods, depending on the media. Analysis was predominantly by gas chromatography/mass spectrometry (GC/MS) or gas chromatography with electron capture detection (GC/ECD). Concentrations of the targeted pollutants were low and well below the levels generally considered to be of concern as possible health hazards. Potential exposures to the target compounds were estimated from the concentrations in the various media, the children's daily time-activity schedules at day care, and the best currently available estimates of the inhalation rates (8.3 m(3)/day) and soil ingestion rates (100 mg/day) of children ages 3-5. The potential exposures for the target compounds differed depending on the compound class and the sampled media.

Potential exposures through dietary ingestion were greater than those through inhalation, which were greater than those through nondietary ingestion, for the total of all PAHs, the phenols, the organophosphate pesticides, and the organochlorine pesticides. Potential exposures through dietary ingestion were greater than those through nondietary ingestion, which were greater than those through inhalation, for those PAHs that are probable human carcinogens (B2 PAH), the phthalate esters, and 2,4D. For the PCBs, exposures through inhalation were greater than those through nondietary ingestion, and exposures through dietary ingestion were smallest. Differences in targeted compound levels between the centers that serve mainly low-income clients and those that serve mainly middle-income clients were small and depended on the compound class and the medium.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2009","Bakke, B., De Roos, A. J., Barr, D. B., Stewart, P. A., Blair, A., Freeman, L. B., Lynch, C. F., Allen, R. H., Alavanja, M. C., Vermeulen, R.","Exposure to atrazine and selected non-persistent pesticides among corn farmers during a growing season","Journal of exposure science & environmental epidemiology","19(6):544-54","c136c53e-895c-498e-a076-6a898db3d026","","The aim was to develop quantitative estimates of farmers' pesticide exposure to atrazine and to provide an overview of background levels of selected non-persistent pesticides among corn farmers in a longitudinal molecular epidemiologic study. The study population consisted of 30 Agricultural Health Study farmers from Iowa and 10 non-farming controls. Farmers completed daily and weekly diaries from March to November in 2002 and 2003 on pesticide use and other exposure determinants. Urine samples were collected at 10 time points relative to atrazine application and other farming activities. Pesticide exposure was assessed using urinary metabolites and diaries. The analytical limit of detection (LOD) ranged between 0.1 and 0.2 microg/l for all pesticide analytes except for isazaphos (1.5 microg/l) and diazinon (0.7 microg/l). Farmers had higher geometric mean urinary atrazine mercapturate (AZM) values than controls during planting (1.1 vs <LOD microg/g creatinine; P<0.05). AZM levels among farmers were significantly related to the amount of atrazine applied (P=0.015). Interestingly, farmers had a larger proportion of samples above the LOD than controls even after exclusion of observations with an atrazine application within 7 days before urine collection (38% vs 6%, P<0.0001). A similar pattern was observed for 2,4-D and acetochlor (92% vs 47%, P<0.0001 and 45% vs 4%, P<0.0001, respectively). Urinary AZM levels in farmers were largely driven by recent application of atrazine. Therefore, the amount of atrazine applied is likely to provide valid surrogates of atrazine exposure in epidemiologic studies. Elevated background levels of non-persistent pesticides, especially 2,4-D, indicate importance in epidemiologic studies of capturing pesticide exposures that might not be directly related to the actual application.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2005","Phuntuwate, W., Suthisisang, C., Koanantakul, B., Mackness, M. I., Mackness, B.","Paraoxonase 1 status in the Thai population","Journal of human genetics","50(6):293-300","d45b4be5-4a07-42f8-a965-52d6c5ed6628","","Human serum paraoxonase 1 (PON1), a high-density lipoprotein (HDL)-associated enzyme, has been shown to reduce the oxidation of low-density lipoprotein (LDL) and HDL by degrading lipid peroxides. This property of PON1 accounts for its ability to protect against atherosclerosis. In this study, we identified four polymorphisms in both the coding (L55M and Q192R) and regulatory regions (T-108C and G-

909C) of the human PON1 gene in 202 healthy Thai individuals and investigated the influence of these polymorphisms on serum PON1 activity towards three substrates, namely, paraoxon, phenylacetate and diazoxon. The PON1 L55M, Q192R and G-909C polymorphisms significantly affected the variation in serum PON1 activity towards paraoxon. Serum PON1 activity towards paraoxon was significantly different among the genotype groups, as follows: 55LL > 55LM/55MM, 192RR > 192QR > 192QQ and -909CC > -909CG > -909GG. The PON1 Q192R and G-909C polymorphisms also influenced the variation in serum PON1 activity towards diazoxon but in the opposite direction to the activity towards paraoxon. Only the PON1 L55M polymorphism was associated with significant variation in serum PON1 activity towards phenylacetate while the PON1 T-108C polymorphism had no significant effect on serum PON1 activity towards any substrate. We also found linkage disequilibrium among the polymorphic sites, including Q192R versus L55M, Q192R versus T-108C and Q192R versus G-909C. Serum PON1 activity towards both paraoxon and phenylacetate, but not diazoxon, was positively correlated with HDL cholesterol (HDL-C) and apo AI concentrations. None of the PON1 polymorphisms significantly affected serum lipid, lipoprotein or apolipoprotein concentrations. Our findings suggest that the physiological relevance of the PON1 polymorphisms is that they are associated with significant differences in serum PON1 activity, and the impact of PON1 polymorphisms on this activity is substrate-dependent.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Oostingh, G. J., Wichmann, G., Schmittner, M., Lehmann, I., Duschl, A.","The cytotoxic effects of the organophosphates chlorpyrifos and diazinon differ from their immunomodulating effects","Journal of immunotoxicology","6(2):136-45","300b86c5-bb86-4f87-a5d8-bc3a36960ee0","","Some organophosphate insecticides have immunomodulating capacities, but it is unknown whether different compounds within this class affect the immune system to the same extent. In this in vitro study, human immortalized T-lymphocytes or bronchial epithelial cells were treated with diazinon or chlorpyrifos in the absence or presence of cellular stress factors, thereby mimicking a stimulated immune system. Cytotoxicity was determined and cytokine release or cytokine-promoter studies were performed to study immunomodulatory effects of these chemicals, whereby the same concentrations of chlorpyrifos and diazinon were used. Results showed that chlor- pyrifos was cytotoxic at concentrations >/= 250 muM, whereas diazinon was not toxic at concentrations up to 1 mM. The immunomodulatory effects of these two compounds were similar for most cytokine promoters tested and induction of cellular stress enhanced these effects. The results were compared to data obtained with blood mononuclear cells, which confirmed the results of stably transfected cell lines, but refer to a higher sensitivity of primary cells. In conclusion, these two pesticides act in a different manner on cell viability and on some immune parameters, but cell viability was not linked to immunomodulation. The results also imply that healthy and diseased individuals are differentially affected by these pollutants.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Goldner, W. S., Sandler, D. P., Yu, F., Shostrom, V., Hoppin, J. A., Kamel, F., LeVan, T. D.","Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study","Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine","55(10):1171-8","ee9da7aa-c461-4674-873c-876433fe791c","","OBJECTIVE: Evaluate the association between thyroid disease and use of insecticides, herbicides, and fumigants/fungicides in male applicators in the

Agricultural Health Study. METHODS: We examined the association between use of 50 specific pesticides and self-reported hypothyroidism, hyperthyroidism, and ""other"" thyroid disease among 22,246 male pesticide applicators. RESULTS: There was increased odds of hypothyroidism with ever use of the herbicides 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), 2,4,5-TP (2,4,5-trichlorophenoxy-propionic acid), alachlor, dicamba, and petroleum oil. Hypothyroidism was also associated with ever use of eight insecticides: organochlorines chlordane, dichlorodiphenyltrichloroethane (DDT), heptachlor, lindane, and toxaphene; organophosphates diazinon and malathion; and the carbamate carbofuran. Exposure-response analysis showed increasing odds with increasing level of exposure for the herbicides alachlor and 2,4-D and the insecticides aldrin, chlordane, DDT, lindane, and parathion. CONCLUSION: There is an association between hypothyroidism and specific herbicides and insecticides in male applicators, similar to previous results for spouses.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Pahwa, P., Karunanayake, C. P., Dosman, J. A., Spinelli, J. J., McLaughlin, J. R.","Soft-tissue sarcoma and pesticides exposure in men: results of a Canadian case-control study","Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine","53(11):1279-86","15922690-34d1-4961-b48b-706c9e8f9752","","OBJECTIVES: The objective was to investigate the putative associations of specific pesticides with soft-tissue sarcoma (STS). METHODS: A Canadian population-based case-control study conducted in six provinces was used in this analysis. The study design consisted of two stages: a self-administered postal questionnaire and a telephone interview for those reporting pesticides exposure of 10 hours per year or more; and a 15% random sample of the remainder. Conditional logistic regression was used to fit the statistical models. RESULTS: A positive history of cancer among first-degree relatives and exposure to aldrin and diazinon were statistically significant independent predictors of an increased risk for STS, whereas diagnosis of whopping cough lowered the risk of STS. CONCLUSIONS: The incidence of STS was associated with specific insecticides after adjustment for other independent predictors.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Slager, R. E., Simpson, S. L., Levan, T. D., Poole, J. A., Sandler, D. P., Hoppin, J. A.","Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study","Journal of toxicology and environmental health. Part A","73(20):1382-93","a64e52a7-3836-4123-93a3-a5134d473f2a","","Farmers commonly experience rhinitis but the risk factors are not well characterized. The aim of this study was to analyze cross-sectional data on rhinitis in the past year and pesticide use from 21,958 Iowa and North Carolina farmers in the Agricultural Health Study, enrolled 1993-1997, to evaluate pesticide predictors of rhinitis. Polytomous and logistic regression models were used to assess association between pesticide use and rhinitis while controlling for demographics and farm-related exposures. Sixty-seven percent of farmers reported current rhinitis and 39% reported 3 or more rhinitis episodes. The herbicides glyphosate [odds ratio (OR) = 1.09, 95% confidence interval (95% CI) = 1.05-1.13] and petroleum oil (OR = 1.12, 95% CI = 1.05-1.19) were associated with current rhinitis and increased rhinitis episodes. Of the insecticides, four organophosphates (chlorpyrifos, diazinon, dichlorvos, and malathion), carbaryl, and use of permethrin on animals were predictors of current rhinitis. Diazinon was significant in the overall polytomous model and was associated with an elevated OR of 13+ rhinitis episodes (13+ episodes OR

= 1.23, 95% CI = 1.09-1.38). The fungicide captan was also a significant predictor of rhinitis. Use of petroleum oil, use of malathion, use of permethrin, and use of the herbicide metolachlor were significant in exposure-response polytomous models. Specific pesticides may contribute to rhinitis in farmers; agricultural activities did not explain these findings.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Von Stackelberg, K.","A systematic review of carcinogenic outcomes and potential mechanisms from exposure to 2,4-D and MCPA in the environment","","2013","ab7e17f2-32f5-42a6-8522-b6ae5b6e3557","","Chlorophenoxy compounds, particularly 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxy)acetic acid (MCPA), are amongst the most widely used herbicides in the United States for both agricultural and residential applications. Epidemiologic studies suggest that exposure to 2,4-D and MCPA may be associated with increased risk non-Hodgkins lymphoma (NHL), Hodgkin's disease (HD), leukemia, and soft-tissue sarcoma (STS). Toxicological studies in rodents show no evidence of carcinogenicity, and regulatory agencies worldwide consider chlorophenoxies as not likely to be carcinogenic or unclassifiable as to carcinogenicity. This systematic review assembles the available data to evaluate epidemiologic, toxicological, pharmacokinetic, exposure, and biomonitoring studies with respect to key cellular events noted in disease etiology and how those relate to hypothesized modes of action for these constituents to determine the plausibility of an association between exposure to environmentally relevant concentrations of 2,4-D and MCPA and lymphohematopoietic cancers. The combined evidence does not support a genotoxic mode of action. Although plausible hypotheses for other carcinogenic modes of action exist, a comparison of biomonitoring data to oral equivalent doses calculated from bioassay data shows that environmental exposures are not sufficient to support a causal relationship. Genetic polymorphisms exist that are known to increase the risk of developing NHL. The potential interaction between these polymorphisms and exposures to chlorophenoxy compounds, particularly in occupational settings, is largely unknown. Â© 2013 Katherine von Stackelberg.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Alavanja, M. C. R., Bonner, M. R.","Occupational pesticide exposures and cancer risk: A review","","15(4):238-263","0a271fb8-39e7-48bc-9f89-189f52a45de7","","A review of the epidemiological literature linking pesticides to cancers in occupational studies worldwide was conducted, with particular focus on those articles published after the release of IARC Monograph 53 (1991): Occupational Exposures in Insecticide Applications and Some Pesticides. Important new data are now available. Chemicals in every major functional class of pesticides including insecticides, herbicide, fungicides, and fumigants have been observed to have significant associations with an array of cancer sites. Moreover, associations were observed with specific chemicals in many chemical classes of pesticides such as chlorinated, organophosphate, and carbamate insecticides and phenoxy acid and triazine herbicides. However, not every chemical in these classes was found to be carcinogenic in humans. Twenty-one pesticides identified subsequent to the last IARC review showed significant exposure-response associations in studies of specific cancers while controlling for major potential confounders. This list is not an exhaustive review and many of these observations need to be evaluated in other epidemiological studies and in conjunction with data from toxicology and cancer biology. Nonetheless, it is reasonable and timely for the scientific community to provide a multidisciplinary expert review and evaluation of these pesticides and their potential to produce cancer

in occupational settings. Â© 2012 Copyright Taylor and Francis Group, LLC.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Neafsey, P., Ginsberg, G., Hattis, D., Sonawane, B.","Genetic polymorphism in cytochrome P450 2D6 (CYP2D6): Population distribution of CYP2D6 activity","","12(5-6):334-361","e1eff7d5-dcde-4b76-9ff9-6872eb28e839","","Cytochrome P-450 2D6 (CYP2D6) is involved in the metabolism of many therapeutic drugs even though the enzyme represents a small proportion of the total CYP content of human liver. In vivo phenotyping with probe drug substrates such as debrisoquine and dextromethorphan showed a clear separation between poor metabolizers (PM) and extensive metabolizers (EM). This polymorphism may affect susceptibility to environmental disease, as suggested by molecular epidemiologic studies that found an association between CYP2D6 metabolizer phenotype and cancer risk; however, this association is not consistent. There are only a few examples of CYP2D6 involvement in toxicant mechanism of action, but this has not been extensively studied. Gene probe studies documented a number of genetic polymorphisms that underlie CYP2D6 metabolizer phenotypes. The EM group carries the wild-type (*1) or active (*2) variant alleles, while the PM group carries the*3,*4,*5, or*6 alleles, all of which code for a protein that has lower or null CYP2D6 activity. The current analysis characterizes (a) influence of genotype on phenotype based upon in vivo metabolism studies of probe drugs and (b) frequency of the major genotypes in different population groups is also characterized. These data were then incorporated into Monte Carlo modeling to simulate population distributions of CYP2D6 activity. This analysis reproduced the bimodal distributions commonly seen in phenotyping studies of Caucasians and found extensive population variability in enzyme activity, as indicated by the 9- to 56-fold difference between the PM modal median and the total population median CYP2D6 activity. This substantial degree of interindividual variability in CYP function indicates that assessments involving CYP2D6 substrates need to consider the full distribution of enzyme activity in refining estimates of internal dose in health assessments of xenobiotics.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Guyton, K. Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Mattock, H., Straif, K.","Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate","The Lancet. Oncology","16(5):490-1","089d2b00-601e-4b2a-8655-ab05fb01261d","","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Guyton, K. Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Mattock, H., Straif, K., Blair, A., Fritschi, L., McLaughlin, J., Sergi, C. M., Calaf, G. M., Le Curieux, F., Baldi, I., Forastiere, F., Kromhout, H., t Mannetje, A., Rodriguez, T., Egeghy, P., Jahnke, G. D., Jameson, C. W., Martin, M. T., Ross, M. K., Rusyn, I., Zeise, L.","Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate","","16(5):490-491","ea3bede5-1f9e-48ac-bec7-5cd7b29a4e85","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Ajmal, K., Azmi, M. A., Zaidi, I. H., Naqvi, S. N. H., Perveen, R., Azmi, M. A.","Organophosphate and pyrethroid residues in the milk of women and breast cancer patients from Karachi","","23(2):63-66","c9235cc6-eb8f-4e25-8dfd-8a92ebe5d6b8","","Aim: The aim of this study was to determine the presence of pesticide residues organophosphate and pyrethroid in the milk of women and in serum of breast cancer patients from different localities of Karachi

due to pesticide exposure. Study Design: An experimental study. Place and Duration of Study: This is a research-based study that was conducted in the Department of Pharmacology, Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi from March 2008 to March 2010. Materials and Methods: A total 40 milk samples were collected from private clinics and 6 serum samples from breast cancer patients were also collected from private cancer hospitals based at different areas of Karachi. All the samples were analyzed for the presence of pesticide residues. Samples of milk and serum were prepared accordingly and the purified samples were injected into the HPLC apparatus. The peaks of the samples were compared by the retention time of the standard peaks. The chromatogram obtained indicated the quantity of pesticide residues. Results: Milk samples and serum samples were analyzed using HPLC technique. Pesticides such as malathion, permethrin, deltamethrin and Polytrin-C were detected in different concentrations. The levels were significantly higher than the maximum residual limit. Conclusion: It is concluded that the presence of pesticides in the human body is a major concern in the development of various ailments because of possible immunotoxic, mutagenic and carcinogenic potential of pesticides.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2000","Hatjian, B. A., Mutch, E., Williams, F. M., Blain, P. G., Edwards, J. W.","Cytogenetic response without changes in peripheral cholinesterase enzymes following exposure to a sheep dip containing diazinon in vivo and in vitro","Mutation research","472(1-2):85-92","fbe97d4c-2132-4f6b-92bf-2578e74fd996","","Occupational exposure to organophosphorus insecticides (OPs), such as diazinon, may be monitored by the measurement of the activity of peripheral cholinesterase enzymes, including erythrocyte acetylcholinesterase (EAChE) and plasma or serum cholinesterase (plasma or serum ChE). Exposures have also been measured by the analysis of dialkyl phosphate metabolites of OPs in urine. The potential health risks associated with exposure, especially those of a neurological nature, may then be estimated, and appropriate measures to reduce or eliminate exposures can be implemented. There is evidence that some OP pesticides may have in vivo genotoxic effects, suggesting a possible link with cancer with long term or repeated heavy exposures. This paper describes work performed in 17 subjects with a single or two exposures to a sheep dip containing diazinon. Urine samples revealed OP metabolites dimethylphosphate (DMP), dimethylthiophosphate (DMTP), diethylphosphate (DEP) and diethylthiophosphate (DETP) in 37% of subjects at low levels which were not elevated after exposure. EAChE and plasma ChE were also unchanged before and after exposure, and were similar to those measured in unexposed control groups. Sister chromatid exchanges (SCE), a marker of chromosome damage, was significantly elevated in peripheral blood lymphocytes after exposure compared with before. SCE were unchanged in a group of non-occupationally exposed workers. In vitro studies with both authentic diazinon (98%) and diazinon in a sheep dip formulation (45%) showed increased SCE and decreased replicative indices, suggesting toxic and genotoxic effects of diazinon.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2005","Kirpnick, Z., Homiski, M., Rubitski, E., Repnevskaya, M., Howlett, N., Aubrecht, J., Schiestl, R. H.","Yeast DEL assay detects clastogens","Mutation research","582(1-2):116-34","6229201a-42bb-4b7a-bf2d-8f9c8249dcc8","","Chromosomal rearrangements, including DNA deletions are involved in carcinogenesis. The deletion (DEL) assay scoring for DNA deletions in the yeast Saccharomyces cerevisiae is able to detect a wide range of carcinogens. Among

approximately 60 compounds of known carcinogenic activity, the DEL assay detected 86% correctly whereas the Ames Salmonella assay detected only 30% correctly [R.J. Brennan, R.H. Schiestl, Detecting carcinogens with the yeast DEL assay, Methods Mol. Biol. 262 (2004) 111-124]. Since the DEL assay is highly inducible by DNA double strand breaks, this study examined the utility of the DEL assay for detecting clastogens. Ten model compounds, with varied mechanisms of genotoxicity, were examined for their effect on the frequency of DNA deletions with the DEL assay. The compounds tested were: actinomycin D, camptothecin, methotrexate and 5-fluorodeoxyuridine, which are anticancer agents, noscapine and furosemide are therapeutics, acridine, methyl acrylate and resorcinol are industrial chemicals and diazinon is an insecticide. The in vitro micronucleus assay (IVMN) in CHO cells, a commonly used tool for detection of clastogens, was performed on the same compounds and the results of the two assays were compared. The results of our study show that there is 70% concordance in the presence of metabolic activation (rat liver S9) and 80% concordance in the absence of metabolic activation between the DEL assay and the standard in vitro micronucleus assay. The lack of cytotoxicity observed for four of the ten compounds examined indicates limited diffusion of lipophilic compounds across the yeast cell wall. Thus, the development of a more permeable yeast tester strain is expected to greatly improve concordance of the DEL assay with the IVMN assay. The yeast DEL assay is inexpensive, amenable to automation and requires less expertise to perform than the IVMN. Thus, it has a strong potential as a robust, fast and economical screen for detecting clastogens in vitro.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Grant, W. F., Owens, E. T.","Zea mays assays of chemical/radiation genotoxicity for the study of environmental mutagens","","613(1):17-64","a1653466-4b45-4496-a02f-9cc7de4e8c31","","From a literature survey, 86 chemicals are tabulated that have been evaluated in 121 assays for their clastogenic effects in Zea mays. Eighty-one of the 86 chemicals are reported as giving a positive reaction (i.e. causing chromosome aberrations). Of these, 36 are reported positive with a dose response. In addition, 32 assays have been recorded for 7 types of radiation, all of which reacted positively. The results of 126 assays with 63 chemicals and 12 types of radiation tested for the inductions of gene mutations are tabulated, as well as 63 chemicals and/or radiation in combined treatments. Three studies reported positive results for mutations on Zea mays seed sent on space flights. The Zea mays (2n = 20) assay is a very good plant bioassay for assessing chromosome damage both in mitosis and meiosis and for somatic mutations induced by chemicals and radiations. The carcinogenicity and Salmonella assays correlate in all cases. The maize bioassay has been shown to be as sensitive and as specific an assay as other plant genotoxicity assays, such as Hordeum vulgare, Vicia faba, Crepis capillaris, Pisum sativum, Lycopersicon esculentum and Allium cepa and should be considered in further studies in assessing clastogenicity. Tests using Zea mays can be made for a spectrum of mutant phenotypes of which many are identifiable in young seedlings. Â© 2006.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Ahmed, M. A., Ahmed, H. I., El-Morsy, E. M.","Melatonin protects against diazinon-induced neurobehavioral changes in rats","Neurochemical research","38(10):2227-36","07e39331-1925-49b2-a0c5-4b9dbd0577cc","","Diazinon is an organophosphorous pesticide with a prominent toxicity on many body organs. Multiple mechanisms contribute to diazinon-induced deleterious effects. Inhibition of acetyl-cholinesterase, cholinergic hyperstimulation, and

formation of reactive oxygen species may play a role. On the other hand, melatonin is a pineal hormone with a well-known potent antioxidant activity and a remarkable modulatory effect on many behavioral processes. The present study revealed that oral diazinon administration (25 mg/kg) increased anxiety behavior in rats subjected to elevated plus maze and open-field tests possibly via the induction of changes in brain monoamines levels (dopamine, norepinephrine, and serotonin). Additionally, brain lipid peroxides measured as malondialdehyde (MDA) and tumor necrosis factor alpha (TNF-alpha) levels were elevated, while the activity of brain glutathione peroxidase enzyme was reduced by diazinon. Co-administration of oral melatonin (10 mg/kg) significantly attenuated the anxiogenic activity of diazinon, rebalanced brain monoamines levels, decreased brain MDA and TNF-alpha levels, and increased the activity of brain glutathione peroxidase enzyme.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Slotkin, T. A., Seidler, F. J.","Does mechanism matter? Unrelated neurotoxicants converge on cell cycle and apoptosis during neurodifferentiation","Neurotoxicology and teratology","34(4):395-402","0b2e378c-db4f-4c08-aa4e-23af245ae487","","Mechanistically unrelated developmental neurotoxicants often produce neural cell loss culminating in similar functional and behavioral outcomes. We compared an organophosphate pesticide (diazinon), an organochlorine pesticide (dieldrin) and a metal (Ni(2+)) for effects on the genes regulating cell cycle and apoptosis in differentiating PC12 cells, an in vitro model of neuronal development. Each agent was introduced at 30muM for 24 or 72h, treatments devoid of cytotoxicity. Using microarrays, we examined the mRNAs encoding nearly 400 genes involved in each of the biological processes. All three agents targeted both the cell cycle and apoptosis pathways, evidenced by significant transcriptional changes in 40-45% of the cell cycle-related genes and 30-40% of the apoptosis-related genes. There was also a high degree of overlap as to which specific genes were affected by the diverse agents, with 80 cell cycle genes and 56 apoptosis genes common to all three. Concordance analysis, which assesses stringent matching of the direction, magnitude and timing of the transcriptional changes, showed highly significant correlations for pairwise comparisons of all the agents, for both cell cycle and apoptosis. Our results show that otherwise disparate developmental neurotoxicants converge on common cellular pathways governing the acquisition and programmed death of neural cells, providing a specific link to cell deficits. Our studies suggest that identifying the initial mechanism of action of a developmental neurotoxicant may be strategically less important than focusing on the pathways that converge on common final outcomes such as cell loss.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Slotkin, T. A., Seidler, F. J.","Developmental neurotoxicity of organophosphates targets cell cycle and apoptosis, revealed by transcriptional profiles in vivo and in vitro","Neurotoxicology and teratology","34(2):232-41","a10aacc6-a23e-41e3-9b90-19db89656610","","Developmental organophosphate exposure reduces the numbers of neural cells, contributing to neurobehavioral deficits. We administered chlorpyrifos or diazinon to newborn rats on postnatal days 1-4, in doses straddling the threshold for barely-detectable cholinesterase inhibition, and evaluated gene expression in the cell cycle and apoptosis pathways on postnatal day 5. Both organophosphates evoked transcriptional changes in 20-25% of the genes in each category; chlorpyrifos and diazinon targeted the same genes, with similar magnitudes of change, as evidenced by high concordance. Furthermore, the same effects were obtained with doses above or below the threshold for

cholinesterase inhibition, indicating a mechanism unrelated to anticholinesterase actions. We then evaluated the effects of chlorpyrifos in undifferentiated and differentiating PC12 cells and found even greater targeting of cell cycle and apoptosis genes, affecting up to 40% of all genes in the pathways. Notably, the genes affected in undifferentiated cells were not concordant with those in differentiating cells, pointing to dissimilar outcomes dependent on developmental stage. The in vitro model successfully identified 60-70% of the genes affected by chlorpyrifos in vivo, indicating that the effects are exerted directly on developing neural cells. Our results show that organophosphates target the genes regulating the cell cycle and apoptosis in the developing brain and in neuronotypic cells in culture, with the pattern of vulnerability dependent on the specific stage of development. Equally important, these effects do not reflect actions on cholinesterase and operate at exposures below the threshold for any detectable inhibition of this enzyme.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Slotkin, T. A., Seidler, F. J., Fumagalli, F.","Unrelated developmental neurotoxicants elicit similar transcriptional profiles for effects on neurotrophic factors and their receptors in an in vitro model","Neurotoxicology and teratology","32(1):42-51","519d88fc-98f8-4c6b-956b-c6c195c9fae2","","Diverse developmental neurotoxicants can often produce similar functional and behavioral outcomes. We examined an organophosphate pesticide (diazinon), an organochlorine pesticide (dieldrin) and a metal (Ni(2+)) for effects on the expression of neurotrophic factors and their receptors and modulators in differentiating PC12 cells, an in vitro model of neuronal development. Each agent was introduced at 30 microM for 24 or 72 h, treatments devoid of cytotoxicity. Using microarrays, we examined the mRNAs encoding members of the fibroblast growth factor (fgf) family, the neurotrophins (ntfs), brain-derived neurotrophic factor (bdnf), nerve growth factor (ngf), the wnt and fzd gene families, and the receptors and modulators for each class. All three agents evoked highly concordant patterns of effects on genes encoding the fgf family, whereas the correlations were poor for the group comprising bdnf, ngf and their respective receptors. For wnt, fzd and their receptors/modulators, the relationships between diazinon and dieldrin were highly concordant, whereas the effect of Ni(2+) was less similar, albeit still significantly correlated with the others. Our results show that otherwise disparate developmental neurotoxicants converge on common sets of neurotrophic pathways known to control neuronal differentiation, likely contributing to similarities in functional outcomes. Further, cell culture models can provide a useful initial screen to identify members of a given class of compounds that may be greater or lesser risks for developmental neurotoxicity, or to provide an indication of agents in different classes that might produce similar effects.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Harris, W., Sachana, M., Flaskos, J., Hargreaves, A. J.","Neuroprotection from diazinon-induced toxicity in differentiating murine N2a neuroblastoma cells","Neurotoxicology","30(6):958-64","f390437e-5808-4d1b-94ce-fdbecb9ffcb0","","In previous work, the outgrowth of axon-like processes by differentiating mouse N2a neuroblastoma cells was shown to be inhibited by exposure to 10 microM diazinon. In the present work, N2a cells were induced to differentiate for 24 h in the presence and absence of 10 microM diazinon and 20% (v/v) conditioned medium derived from differentiating rat C6 glioma cells. Cells were then stained or lysed for morphological and biochemical analyses, respectively.

The data showed that co-treatment with conditioned medium prevented the neurite inhibitory effect of diazinon. Furthermore, a significant recovery was also observed in the reduced levels of neurofilament heavy chain (NFH), heat shock protein-70 (HSP-70) and growth-associated protein-43 (GAP-43) observed as a result of diazinon treatment in the absence of conditioned medium, as seen by densitometric analysis of Western blots of cell lysates probed with monoclonal antibodies N52, BRM-22 and GAP-7B10. By contrast, no significant change was noted in the reactivity of cell lysates with antibodies against alpha- and beta-tubulin under any condition tested. After pre-incubation with a polyclonal anti-glial cell line-derived neurotrophic factor (GDNF) antibody, conditioned medium derived from rat C6 glioma cells lost its ability to protect N2a cells against the neurite inhibitory effects of diazinon. In conclusion, these data demonstrate that C6 conditioned medium protects N2a cells from the neurite inhibitory effects of diazinon by blocking molecular events leading to axon damage and that GDNF is implicated in these effects.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2003","De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., Blair, A.","Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men","Occupational and environmental medicine","60(9):E11","d85d0dc5-def9-4aaf-9eea-785533e90267","","BACKGROUND: An increased rate of non-Hodgkin's lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult. METHODS: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable. RESULTS: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these ""potentially carcinogenic"" pesticides suggested a positive trend of risk with exposure to increasing numbers. CONCLUSION: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Lerro, C. C., Koutros, S., Andreotti, G., Friesen, M. C., Alavanja, M. C., Blair, A., Hoppin, J. A., Sandler, D. P., Lubin, J. H., Ma, X., Zhang, Y., Beane Freeman, L. E.","Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study","Occupational and environmental medicine","72(10):736-44","82200934-d354-415c-87c5-79bfa237bc03","","OBJECTIVES: Organophosphates (OPs) are among the most commonly used insecticides. OPs have been linked to cancer risk in some epidemiological studies, which have been largely conducted in predominantly male populations. We evaluated personal use of specific OPs and cancer incidence among female spouses of pesticide applicators in the prospective Agricultural Health Study cohort. METHODS: At enrolment (1993-1997), spouses provided information about ever use of specific pesticides, including 10 OPs, demographic information, reproductive health history and other potential confounders. We used Poisson regression to estimate relative risks (RRs) and 95% CIs for all cancers diagnosed through 2010 for North Carolina and through

2011 for Iowa. RESULTS: Among 30,003 women, 25.9% reported OP use, and 718 OP-exposed women were diagnosed with cancer during the follow-up period. Any OP use was associated with an elevated risk of breast cancer (RR=1.20, 95% CI 1.01 to 1.43). Malathion, the most commonly reported OP, was associated with increased risk of thyroid cancer (RR=2.04, 95% CI 1.14 to 3.63) and decreased risk of non-Hodgkin lymphoma (RR=0.64, 95% CI 0.41 to 0.99). Diazinon use was associated with ovarian cancer (RR=1.87, 95% CI 1.02 to 3.43). CONCLUSIONS: We observed increased risk with OP use for several hormonally-related cancers, including breast, thyroid and ovary, suggesting potential for hormonally-mediated effects. This study represents the first comprehensive analysis of OP use and cancer risk among women, and thus demonstrates a need for further evaluation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Alavanja, M., Hofmann, J., Lynch, C., Hines, C., Barry, K., Barker, J., Buckman, D., Thomas, K., Sandler, D., Hoppin, J., Koutros, S., Andreotti, G., Lubin, J., Blair, A., Freeman, L. B.","Occupational use of insecticides, fungicides and fumigants and risk of non-hodgkin lymphoma and multiple myeloma in the agricultural health Study0286 Occupational use of insecticides, fungicides and fumigants and risk of non-Hodgkin lymphoma and multiple myeloma in the agricultural health study","","71:A36","0f87ca7a-fe93-4dae-8a8c-b9eb8e44297b","","Objectives Farming and exposure to pesticides have been linked to non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) in previous studies. We evaluated use of insecticides, fungicides and fumigants and risk of NHL, including MM and other NHL sub-types in the Agricultural Health Study, a US-based prospective cohort study. Method A total of 527 cases occurred among 55 875 pesticide applicators from enrollment (1993-1997) through 2011 in Iowa and 2010 in North Carolina. Information on pesticide use, other agricultural exposures and other factors was obtained from questionnaires at enrollment and follow-up approximately five years later (1999-2005). Information from these questionnaires was used to create lifetime-days and intensity-weighted lifetime-days of pesticide use. Poisson regression and polytomous logit models were used to calculate relative risks (RR) and 95% confidence intervals (CI) to evaluate associations between 26 pesticides and NHL and five NHL-subtypes including multiple myeloma, while adjusting for potential confounding factors. Results Statistically significant positive exposure-response trends occurred between overall NHL risk and lindane (p-trend = 0.004) and DDT (p-trend = 0.02). In addition, ever use of terbufos was associated with NHL overall (RR=1.2; CI=1.0-1.5), but with no exposure-response trend. In sub-type analyses, terbufos and DDT were associated with small cell lymphoma/chronic lymphocytic leukaemia/marginal cell lymphoma. In addition, lindane and diazinon were associated with follicular lymphoma and permethrin with MM although tests of homogeneity did not show significant differences in exposure-response among NHL-subtypes for any chemical. Conclusions These findings are among the first to suggest links between DDT, lindane, permethrin, diazinon and terbufos and specific NHL subtypes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Andreotti, G., Hoppin, J., Savage, S., Hou, L., Baccarelli, A., Hoxha, M., Koutros, S., Sandler, D., Alavanja, M., Freeman, L. B.","Pesticide use and relative telomere length in the agricultural health study","","71:A14-A15","f1585273-b51f-4858-aeaf-81ff338f213e","","Objectives Epidemiologic studies have linked pesticide use to various health outcomes, including cancer, but underlying mechanisms remain unclear. In a previous analysis from the Agricultural Health Study (AHS), a prospective cohort study of pesticide applicators in

the US, use of certain pesticides was linked to shorter relative telomere length (RTL) measured in buccal cell DNA. In this analysis we examined the associations between occupational pesticide use and RTL measured in blood DNA. Method We conducted an analysis of 80 pesticides and RTL in 568 cancer-free male participants aged 31-94 years in the AHS. We used self-reported pesticide use information collected at study enrollment (1993-1997) and two follow-up questionnaires administered approximately 5 years apart to construct exposure metrics, including intensity-weighted lifetime days (lifetime daysâˆ-intensity score). Blood samples were collected in 2006-2008, and RTL was measured in DNA using qPCR. Multivariable linear regression was used to evaluate the associations between individual pesticide use and RTL, adjusting for age at blood draw and other pesticides associated with RTL. Results Increasing tertiles of intensity-weighted days of alachlor were associated with longer RTL (p-trend = 0.01). In contrast, increasing tertiles of intensity-weighted days of 2,4-D (p-trend = 0.05), diazinon (p-trend = 0.01) and aldrin (p-trend = 0.01) were associated with shorter RTL. Conclusions We found two herbicides (alachlor, 2,4-D) and two insecticides (diazinon, aldrin) significantly associated with alterations in RTL. These pesticides have been linked to increased cancer risk in epidemiological and/or animal studies. Consistent with our finding, shorter RTL with 2,4-D use was previously observed in an analysis of buccal cells in the AHS.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Jones, R. R., Barone-Adesi, F., Koutros, S., Lerro, C. C., Blair, A., Lubin, J., Heltshe, S. L., Hoppin, J. A., Alavanja, M. C. R., Beane Freeman, L. E.","Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agricultural Health Study: An updated analysis","","72(7):496-503","33963536-4d81-4d86-a651-87c160224c7b","","Objective: Diazinon, a common organophosphate insecticide with genotoxic properties, was previously associated with lung cancer in the Agricultural Health Study (AHS) cohort, but few other epidemiological studies have examined diazinon-associated cancer risk. We used updated diazinon exposure and cancer incidence information to evaluate solid tumour risk in the AHS. Methods Male pesticide applicators in Iowa and North Carolina reported lifetime diazinon use at enrolment (1993-1997) and follow-up (1998-2005); cancer incidence was assessed through 2010(North Carolina)/2011(Iowa). Among applicators with usage information sufficient to evaluate exposure-response patterns, we used Poisson regression to estimate adjusted rate ratios (RRs) and 95% CI for cancer sites with â‰¥10 exposed cases for both lifetime (LT) exposure days and intensityweighted (IW) lifetime exposure days (accounting for factors impacting exposure). Results: We observed elevated lung cancer risks (N=283) among applicators with the greatest number of LT (RR=1.60; 95% CI 1.11 to 2.31; P<inf>trend</inf>=0.02) and IW days of diazinon use (RR=1.41; 95% CI 0.98 to 2.04; P<inf>trend</inf>=0.08). Kidney cancer (N=94) risks were nonsignificantly elevated (RR<inf>LT days</inf>=1.77; 95% CI 0.90 to 3.51; P<inf>trend</inf>=0.09; RR<inf>IW days</inf> 1.37; 95% CI 0.64 to 2.92; P<inf>trend</inf>=0.50), as were risks for aggressive prostate cancer (N=656). Conclusions: Our updated evaluation of diazinon provides additional evidence of an association with lung cancer risk. Newly identified links to kidney cancer and associations with aggressive prostate cancer require further evaluation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Jensen, T. K., Bonde, J. P., Joffe, M.","The influence of occupational exposure on male reproductive function","","56(8):544-553","0a2d897a-7012-4685-b212-670017e81252","","Recently, many

studies have found a decrease in semen quality which has increased the focus on male reproductive health. Occupational hazards are by far the best documented in reproductive epidemiological research. Generally, occupational exposures have been divided into physical exposures (heat and radiation), chemical exposures (solvents and pesticides), psychological exposures (distress), exposure to metals and welding. The recent and/or most important epidemiological studies exploring the effect of occupational exposures on semen quality and fecundity, the ability to conceive, are reviewed. The evidence for an adverse effect on male reproduction of several occupational and environmental exposures and toxicants, such as heat, ionizing radiation, inorganic lead, dibromochloropropane, ethylene dibromide, some ethylene glycol ethers, carbon disulfide and welding operations, is strongly supported in well-designed epidemiological studies. For other agents, the association is only suspected or suggested and needs further evaluation before conclusions can be drawn. It is also important to bear in mind that many workers in the non-Western world still are exposed to substances that are banned in the Western world, sometimes in high concentrations. Â© 2006 Oxford University Press.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2013","Pakzad, M., Fouladdel, S., Nili-Ahmadabadi, A., Pourkhalili, N., Baeeri, M., Azizi, E., Sabzevari, O., Ostad, S. N., Abdollahi, M.","Sublethal exposures of diazinon alters glucose homostasis in Wistar rats: Biochemical and molecular evidences of oxidative stress in adipose tissues","Pesticide biochemistry and physiology","105(1):57-61","bdc1b29a-acb2-42a1-9b7c-5c539c1e7efd","","Disorder of glucose homeostasis is one of the most important complications following exposure to organophosphorous (OPs) pesticides. Regarding the importance of adipose tissue in regulating blood glucose and the role of oxidative stress in toxicity of OPs and in the continue of our previous works, in the present study we focused on tumor necrosis factor alpha (TNFalpha), glucose transporter type 4 (GLUT4), and nuclear factor kappa-light-chain-enhancer of activated B cells (Nf-kappaB) in a sublethal model of toxicity by diazinon as a common OPs. Following time-course study of various doses of diazinon in impairing blood glucose, dose of 70mg/kg/day was found the optimum. Animals were treated for 4 weeks and after gavage of glucose (2g/kg), the glucose change was evaluated at time-points of 0, 30, 60, 120 and 180min to identify oral glucose tolerance test (GTT). In addition, serum insulin was measured in fasting condition. In adipose tissue, oxidative stress markers including reactive oxygen species (ROS), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and TNFalpha were evaluated. The mRNA expression of GLUT4, Nf-kappaB and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were also determined by real time reverse transcription polymerase chain reaction (RT-PCR). Diazinon at dose of 70mg/kg/day impaired GTT and diminished insulin level while augmented ROS, NADPH oxidase, and TNFalpha. The GLUT4 mRNA expression was amplified by diazinon while unlikely, the expression of Nf-kappaB gene did not change. On the basis of biochemical and molecular findings, it is concluded that diazinon impairs glucose homeostasis through oxidative stress and related proinflammatory markers in a way to result in a reduced function of insulin inside adipose tissue. Although, diazinon interfered with pancreatic influence on the adipose tissue most probably via stimulation of muscarinic receptors, current data are not sufficient to introduce adipose tissue as a target organ to OPs toxicity. Considering the potential of OPs to accumulate in adipose tissue, it seems a good candidate organ for future studies. Although, hyperglycemia was not induced by diazinon but increased AUC0-180min leads us to the point that diazinon induces kind of

instability in glucose homostasis and
diabetes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Furlong, C. E., Holland, N., Richter, R. J., Bradman, A., Ho, A., Eskenazi, B.","PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity","Pharmacogenetics and genomics","16(3):183-90","a0fac6db-a1cb-45a1-971c-1eaec2ba23a1","","The objective was to determine PON1 status as a predictor for organophosphorus insecticide sensitivity in a cohort of Latina mothers and newborns from the Salinas Valley, California, an area with high levels of organophosphorus insecticide use. PON1 status was established for 130 pregnant Latina women and their newborns using a high-throughput two substrate activity/analysis method which plots rates of diazoxon (DZO) hydrolysis against rates of paraoxon (PO) hydrolysis. Arylesterase activity (AREase) was determined using phenylacetate as a substrate, allowing comparison of PON1 levels across PON1192 genotypes in mothers and children. Phenylacetate hydrolysis is not affected by the Q192R polymorphism. Among newborns, levels of PON1 (AREase) varied by 26-fold (4.3-110.7 U/ml) and among mothers by 14-fold (19.8-281.4 U/ml). On average, children's PON1 levels were four-fold lower than the mothers' PON1 levels (P<0.001). Average PON1 levels in newborns were comparable with reported hPON1 levels in transgenic mice expressing human PON1Q192 or PON1R192, allowing for prediction of relative sensitivity to chlorpyrifos oxon (CPO) and DZO. The predicted range of variability in sensitivity of mothers and children in the same Latino cohort was 65-fold for DZO and 131 to 164-fold for CPO. Overall, these findings indicate that many of the newborns and some of the mothers in this cohort would be more susceptible to the adverse effects of specific organophosphorus pesticide exposure due to their PON1 status. Of particular concern are exposures of pregnant mothers and newborns with low PON1
status.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2003","Mackness, B., Durrington, P., Povey, A., Thomson, S., Dippnall, M., Mackness, M., Smith, T., Cherry, N.","Paraoxonase and susceptibility to organophosphorus poisoning in farmers dipping
sheep","Pharmacogenetics","13(2):81-8","bb4fa286-6961-44fc-b792-bd5e601b41b9","","OBJECTIVES: Human serum paraoxonase (PON1) hydrolyses organophosphate pesticides (OPs) entering the blood circulation and tissue fluid thus limiting toxicity. The PON1 coding region has two polymorphisms involving the amino acids at position 55 (Lt<--M) and 192 (Qt<--R), giving rise to isoenzymes which differ in their catalytic rate for the hydrolysis of OPs. We therefore hypothesized that individuals inheriting low activity isoforms of PON1 would be more liable to report symptoms of OP toxicity. METHODS: We have therefore investigated the relationship between PON1 genetic polymorphisms and PON1 activity in farmers reporting chronic ill health which they attributed to OP exposure whilst sheep dipping (cases) and farmers who carried out similar activities, but remained well (controls). Diazoxon, paraoxon and phenylacetate were used as substrates for PON1. Diazoxon is the active metabolite of diazinon, the sheep dip most commonly used in the UK. RESULTS: Cases were found to be more likely to have the R192 allele (0.01) and to have the L55 allele (0.05) than the controls. This combination of R and L genotypes was associated with lower PON1 activity towards diazoxon in both cases and controls. Farmers in the lowest quintile for the rate of serum diazoxon hydrolysis had a greater risk of being a case i.e. of reporting ill health (odds ratio 2.47 (95% CI 1.35-2.82)), than the other four quintiles of diazoxon hydrolysis. The rate of serum hydrolysis of paraoxon was greatest in cases and controls

with the R/L haplotype (both 0.001). CONCLUSIONS: The farmers reporting chronic ill health due to organophosphate exposure have a higher proportion of the PON1-192R polymorphism associated with lower rates of diazoxon hydrolysis and lower rates of diazoxon hydrolysis than the controls and that their ill health may be explained by a lower ability to detoxify diazoxon.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2014","Alavanja, M. C., Hofmann, J. N., Lynch, C. F., Hines, C. J., Barry, K. H., Barker, J., Buckman, D. W., Thomas, K., Sandler, D. P., Hoppin, J. A., Koutros, S., Andreotti, G., Lubin, J. H., Blair, A., Beane Freeman, L. E.","Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study","PloS one","9(10):e109332","b11a3c44-9480-4e4e-b7da-ec40707bd700","","Farming and pesticide use have previously been linked to non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). We evaluated agricultural use of specific insecticides, fungicides, and fumigants and risk of NHL and NHL-subtypes (including CLL and MM) in a U.S.-based prospective cohort of farmers and commercial pesticide applicators. A total of 523 cases occurred among 54,306 pesticide applicators from enrollment (1993-97) through December 31, 2011 in Iowa, and December 31, 2010 in North Carolina. Information on pesticide use, other agricultural exposures and other factors was obtained from questionnaires at enrollment and at follow-up approximately five years later (1999-2005). Information from questionnaires, monitoring, and the literature were used to create lifetime-days and intensity-weighted lifetime days of pesticide use, taking into account exposure-modifying factors. Poisson and polytomous models were used to calculate relative risks (RR) and 95% confidence intervals (CI) to evaluate associations between 26 pesticides and NHL and five NHL-subtypes, while adjusting for potential confounding factors. For total NHL, statistically significant positive exposure-response trends were seen with lindane and DDT. Terbufos was associated with total NHL in ever/never comparisons only. In subtype analyses, terbufos and DDT were associated with small cell lymphoma/chronic lymphocytic leukemia/marginal cell lymphoma, lindane and diazinon with follicular lymphoma, and permethrin with MM. However, tests of homogeneity did not show significant differences in exposure-response among NHL-subtypes for any pesticide. Because 26 pesticides were evaluated for their association with NHL and its subtypes, some chance finding could have occurred. Our results showed pesticides from different chemical and functional classes were associated with an excess risk of NHL and NHL subtypes, but not all members of any single class of pesticides were associated with an elevated risk of NHL or NHL subtypes. These findings are among the first to suggest links between DDT, lindane, permethrin, diazinon and terbufos with NHL subtypes.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2015","Andreotti, G., Hoppin, J. A., Hou, L., Koutros, S., Gadalla, S. M., Savage, S. A., Lubin, J., Blair, A., Hoxha, M., Baccarelli, A., Sandler, D., Alavanja, M., Beane Freeman, L. E.","Pesticide Use and Relative Leukocyte Telomere Length in the Agricultural Health Study","PloS one","10(7):e0133382","671e1ff3-27c7-42f4-8b5c-d54c64565f99","","Some studies suggest that telomere length (TL) may be influenced by environmental exposures, including pesticides. We examined associations between occupational pesticide use reported at three time points and relative telomere length (RTL) in the Agricultural Health Study (AHS), a prospective cohort study of pesticide applicators in Iowa and North Carolina. RTL was measured by qPCR using leukocyte DNA from 568 cancer-free male AHS participants aged 31-94 years with blood samples collected between 2006 and 2008. Self-reported

information, including pesticide use, was collected at three time points: enrollment (1993-1997) and two follow-up questionnaires (1998-2003, 2005-2008). For each pesticide, we evaluated cumulative use (using data from all three questionnaires), and more recent use (using data from the last follow-up questionnaire). Multivariable linear regression was used to examine the associations between pesticide use (ever, lifetime days, intensity-weighted lifetime days (lifetime days*intensity score)) and RTL, adjusting for age at blood draw and use of other pesticides. Of the 57 pesticides evaluated with cumulative use, increasing lifetime days of 2,4-D (p-trend=0.001), diazinon (p-trend=0.002), and butylate (p-trend=0.01) were significantly associated with shorter RTL, while increasing lifetime days of alachlor was significantly associated with longer RTL (p-trend=0.03). Only the association with 2,4-D was significant after adjustment for multiple comparisons. Of the 40 pesticides evaluated for recent use, malathion was associated with shorter RTL (p=0.03), and alachlor with longer RTL (p=0.03). Our findings suggest that leukocyte TL may be impacted by cumulative use and recent use of certain pesticides.","","","RefMan","","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2014","Lee, W. J., Kim, S. C., Lee, S. J., Lee, J., Park, J. H., Yu, K. S., Lim, J., Kwon, S. W.","Investigating the different mechanisms of genotoxic and non-genotoxic carcinogens by a gene set analysis","","9(1)","b48bf3e8-afd8-4b4e-9724-34cbca863a37","","Based on the process of carcinogenesis, carcinogens are classified as either genotoxic or non-genotoxic. In contrast to non-genotoxic carcinogens, many genotoxic carcinogens have been reported to cause tumor in carcinogenic bioassays in animals. Thus evaluating the genotoxicity potential of chemicals is important to discriminate genotoxic from non-genotoxic carcinogens for health care and pharmaceutical industry safety. Additionally, investigating the difference between the mechanisms of genotoxic and non-genotoxic carcinogens could provide the foundation for a mechanism-based classification for unknown compounds. In this study, we investigated the gene expression of HepG2 cells treated with genotoxic or non-genotoxic carcinogens and compared their mechanisms of action. To enhance our understanding of the differences in the mechanisms of genotoxic and non-genotoxic carcinogens, we implemented a gene set analysis using 12 compounds for the training set (12, 24, 48 h) and validated significant gene sets using 22 compounds for the test set (24, 48 h). For a direct biological translation, we conducted a gene set analysis using Globaltest and selected significant gene sets. To validate the results, training and test compounds were predicted by the significant gene sets using a prediction analysis for microarrays (PAM). Finally, we obtained 6 gene sets, including sets enriched for genes involved in the adherens junction, bladder cancer, p53 signaling pathway, pathways in cancer, peroxisome and RNA degradation. Among the 6 gene sets, the bladder cancer and p53 signaling pathway sets were significant at 12, 24 and 48 h. We also found that the DDB2, RRM2B and GADD45A, genes related to the repair and damage prevention of DNA, were consistently up-regulated for genotoxic carcinogens. Our results suggest that a gene set analysis could provide a robust tool in the investigation of the different mechanisms of genotoxic and non-genotoxic carcinogens and construct a more detailed understanding of the perturbation of significant pathways. Â© 2014 Lee et al.","","","RefMan","","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2013","Thomas, R., Thomas, R. S., Auerbach, S. S., Portier, C. J.","Biological Networks for Predicting Chemical Hepatocarcinogenicity Using Gene Expression Data from Treated Mice and Relevance across

Human and Rat Species","","8(5)","8913d87b-22d5-4767-b670-b28412defe67","","Background:Several groups have employed genomic data from subchronic chemical toxicity studies in rodents (90 days) to derive gene-centric predictors of chronic toxicity and carcinogenicity. Genes are annotated to belong to biological processes or molecular pathways that are mechanistically well understood and are described in public databases.Objectives:To develop a molecular pathway-based prediction model of long term hepatocarcinogenicity using 90-day gene expression data and to evaluate the performance of this model with respect to both intra-species, dose-dependent and cross-species predictions.Methods:Genome-wide hepatic mRNA expression was retrospectively measured in B6C3F1 mice following subchronic exposure to twenty-six (26) chemicals (10 were positive, 2 equivocal and 14 negative for liver tumors) previously studied by the US National Toxicology Program. Using these data, a pathway-based predictor model for long-term liver cancer risk was derived using random forests. The prediction model was independently validated on test sets associated with liver cancer risk obtained from mice, rats and humans.Results:Using 5-fold cross validation, the developed prediction model had reasonable predictive performance with the area under receiver-operator curve (AUC) equal to 0.66. The developed prediction model was then used to extrapolate the results to data associated with rat and human liver cancer. The extrapolated model worked well for both extrapolated species (AUC value of 0.74 for rats and 0.91 for humans). The prediction models implied a balanced interplay between all pathway responses leading to carcinogenicity predictions.Conclusions:Pathway-based prediction models estimated from sub-chronic data hold promise for predicting long-term carcinogenicity and also for its ability to extrapolate results across multiple species.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2011","Band, P. R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R. P., Le, N. D.","Prostate cancer risk and exposure to pesticides in British Columbia Farmers","","71(2):168-183","0dbf3382-093e-4606-bfde-0ed06e273f51","","Background Several epidemiologic studies have reported an increased risk of prostate cancer among farmers. Our aim was to assess the risk of developing prostate cancer in relation to exposure to specific active compounds in pesticides. METHOD A case-control approach was used with 1,516 prostate cancer patients and 4,994 age-matched internal controls consisting of all other cancer sites excluding lung cancer and cancers of unknown primary site. Lifetime occupational history was obtained through a self-administered questionnaire and used in conjunction with a job exposure matrix to estimate the participants' lifetime cumulative exposure to approximately 180 active compounds in pesticides. Conditional logistic regression was used to assess prostate cancer risk, adjusting for potential confounding variables and effect modifiers. These include age, ethnicity, alcohol consumption, smoking, education, and proxy respondent. RESULTS AND CONCLUSIONS The significant association between prostate cancer risk and exposure to DDT (OR=1.68; 95% CI: 1.04-2.70 for high exposure), simazine (OR=1.89; 95% CI: 1.08-3.33 for high exposure), and lindane (OR=2.02; 95% CI: 1.15-3.55 for high exposure) is in keeping with those previously reported in the literature. We also observed a significant excess risk for several active ingredients that have not been previously reported in the literature such as dichlone, dinoseb amine, malathion, endosulfan, 2,4-D, 2,4-DB, and carbaryl. Some findings in our study were not consistent with those reported in the literature, including captan, dicamba, and diazinon. It is possible that these findings showed a real association and the inconsistencies reflected differences of characteristics between study populations. Â©

2010 Wiley-Liss, Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Oh, Y. J., Jung, Y. J., Kang, J. W., Yoo, Y. S.","Investigation of the estrogenic activities of pesticides from Pal-dang reservoir by in vitro assay","","388(1-3):8-15","4b09edff-f46b-4b45-b067-5f989ab771e9","","Endocrine disruptors, when absorbed into the body, interfere with the normal function by mimicking or blocking the hormone system. To investigate compounds mimicking estrogen in the drinking water source of the residence of Seoul, the Pal-dang reservoir was monitored over a period of 5Â years, between 2000 and 2004. Nine kinds of pesticide (carbaryl, DBCP, diazinon, fenitrothion, fenobucarb, flutolanil, iprobenphos, isoprothiolane and parathion) were found to exist in the river water sample. These compounds were detected at low concentrations in the water samples. The total concentration and those of each of these pesticides were below the permissible limits of the National Institute of Environmental Research (NIER), Korea. The estrogenic potencies of the nine pesticides were examined using an E-screen assay with MCF-7 BUS estrogen receptor (ER)-positive human breast cancer cells, with ER-negative MDA MB 231 cell lines also used to compare the results. From this, flutolanil and isoprothiolane were confirmed to have estrogenic activities as shown by the increasing MCF-7 BUS cell growth on their addition. In addition, the estrogen receptor alpha (ERÎ±) protein, estrogen receptor-regulated progesterone receptor (PR) and pS2 mRNA levels on the addition of flutolanil and isoprothiolane were measured with MCF-7 BUS cells. It was observed that the levels of ERÎ± protein decreased and those of the PR and pS2 genes increased on the addition of either flutolanil or isoprothiolane at concentrations of 10- 4Â M, in the same manner as with the addition of 17Î²-estradiol, which was used as the positive control. From these results, it was confirmed that flutolanil and isoprothiolane exhibit estrogenic activities, suggesting they might act through estrogen receptors. Â© 2007.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Sugeng, A. J., Beamer, P. I., Lutz, E. A., Rosales, C. B.","Hazard-ranking of agricultural pesticides for chronic health effects in Yuma County, Arizona","","463-464:35-41","0c85950c-5431-4a0a-8c86-7799089e4f02","","With thousands of pesticides registered by the United States Environmental Protection Agency, it not feasible to sample for all pesticides applied in agricultural communities. Hazard-ranking pesticides based on use, toxicity, and exposure potential can help prioritize community-specific pesticide hazards. This study applied hazard-ranking schemes for cancer, endocrine disruption, and reproductive/developmental toxicity in Yuma County, Arizona. An existing cancer hazard-ranking scheme was modified, and novel schemes for endocrine disruption and reproductive/developmental toxicity were developed to rank pesticide hazards. The hazard-ranking schemes accounted for pesticide use, toxicity, and exposure potential based on chemical properties of each pesticide. Pesticides were ranked as hazards with respect to each health effect, as well as overall chronic health effects. The highest hazard-ranked pesticides for overall chronic health effects were maneb, metam-sodium, trifluralin, pronamide, and bifenthrin. The relative pesticide rankings were unique for each health effect. The highest hazard-ranked pesticides differed from those most heavily applied, as well as from those previously detected in Yuma homes over a decade ago. The most hazardous pesticides for cancer in Yuma County, Arizona were also different from a previous hazard-ranking applied in California. Hazard-ranking schemes that take into account pesticide use, toxicity, and exposure potential can help prioritize pesticides of greatest health risk in agricultural communities. This study

is the first to provide pesticide hazard-rankings for endocrine disruption and reproductive/developmental toxicity based on use, toxicity, and exposure potential. These hazard-ranking schemes can be applied to other agricultural communities for prioritizing community-specific pesticide hazards to target decreasing health risk. Â© 2013 Elsevier B.V.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2010","Flampouri, K., Mavrikou, S., Kintzios, S., Miliadis, G., Aplada-Sarlis, P.","Development and validation of a cellular biosensor detecting pesticide residues in tomatoes","Talanta","80(5):1799-804","07219946-4614-4bf5-923b-4da14bed79ab","","Two of the most important categories of pesticides used in agricultural practice are organophosphates and dithiocarbamates. Their extensive and inappropriate use has rendered their reliable monitoring at trace levels more and more necessary. This study presents the construction of a rapid and sensitive cellular biosensor test based on the measurement of changes of the cell membrane potential of immobilized cells, according to the working principle of the Bioelectric Recognition Assay (BERA). The cells were immobilized by entrapment in a sodium alginate bead and directly applied in different pesticide dilutions and agricultural samples. The pesticides used were the organophosphate insecticide diazinon and the dithiocarbamate fungicide propineb. Two different cell types, N2a (neuroblastoma) and Vero (fibroblast) were used as the biosensory elements in order to investigate their differential response against the pesticides. In this way, we hoped to increase the selectivity of the assay. Based on the observed patterns of response, we demonstrate that the sensor can be used for the qualitative and, in some concentrations, quantitative detection of the pesticides with a high degree of reproducibility. The lowest detected concentration was 3nM. Finally, for the investigation of the effects of different pesticides on the accumulation of cytosolic Ca(2+), we conducted a fluorescent assay on N2a cells treated with tomato sample extracts, which were replicates of the E.U. proficiency test sample. The tomato samples were either organically grown or contained 14 different pesticides. The experimental results showed a higher increase of the intracellular Ca(2+) concentration in cells treated with non-organic samples compared to the cells treated with organic samples.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2012","Mu, X., Yu, N., Wang, C., Zou, X., Abulimite, Z., Xia, Z.","Evaluation of a new substrate for measurement of serum PON arylesterase activity","Talanta","88:711-6","b622e9b1-b879-47f7-a9d6-f0a8343868b8","","It was found that the hydrolysis of 9-(4-chlorophenyloxycarbonyl)-10-methylacridinium triflate (CPOCMA) could be catalyzed by recombinant human PON1. Based on this property, the CPOCMA was evaluated as a substrate for serum PON activity assay. The apparent K(m) value of a serum sample for the substrate was determined as 85nmol/L, close to the K(m) value (83nmol/L) of rHuPON1. The interferences by other esterase such as acetylcholinerase and lipases were investigated. The NaCl and CaCl(2) as PON activity enhancers were able to improve the specific signal, respectively. The rHuPON1 in presence of CaCl(2) showed at least 7.8 times selectivity over acetylcholinerase and lipases. By comparing with the UV methods based on phenyl acetate and diazinon, respectively, the proposed chemiluminescent method was validated with 30 serum samples. The method based on CPOCMA allows reliable, cost-saving, and specific determination in a buffer of physiological pH.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","1995","Kato, T., Ogiso, T., Kato, K., Sano, M., Hasegawa, R., Shirai, T., Ito, N.","Lack of promoting activity of four

pesticides on induction of preneoplastic liver cell foci in rats","Teratogenesis, carcinogenesis, and mutagenesis","15(5):251-7","ecfe1fb3-059a-48b2-bbc6-e0d0a6752613","","Four pesticides were examined for hepatopromoting activity using a medium-term bioassay based upon induction of glutathione S-transferase placental form (GST-P) positive foci in the rat liver. Male F344 rats were initially injected with diethylnitrosamine (DEN; 200 mg/kg body weight) intraperitoneally and 2 weeks later were treated with O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN; 75 and 150 ppm), diazinon (500 and 1,000 ppm), phenthoate (500 and 1,000 ppm), or iprobenfos (500 and 1,000 ppm) in the diet for 6 weeks and then killed, all rats being subjected to partial hepatectomy at week 3. All of the pesticides gave negative results, the numbers and areas of GST-P positive foci not exceeding the control values for animals given DEN alone. Indeed, a significant reduction of foci development was seen for EPN (75 ppm). These findings provide experimental evidence that the presently examined four pesticides do not have hepatocarcinogenic potential in rats.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2007","Flaskos, J., Harris, W., Sachana, M., Munoz, D., Tack, J., Hargreaves, A. J.","The effects of diazinon and cypermethrin on the differentiation of neuronal and glial cell lines","Toxicology and applied pharmacology","219(2-3):172-80","6990d1de-26ec-4e41-b13f-5dfd104f159e","","Diazinon and cypermethrin are pesticides extensively used in sheep dipping. Diazinon is a known anti-cholinesterase, but there is limited information regarding its molecular mechanism of action. This paper describes the effects of diazinon and cypermethrin at a morphological and molecular level on differentiating mouse N2a neuroblastoma and rat C6 glioma cell lines. Concentrations up to 10 microM of both compounds and their mixture had no effect on the viability of either cell line, as determined by methyl blue tetrazolium reduction and total protein assays. Microscopic analysis revealed that 1 microM and 10 microM diazinon but not cypermethrin inhibited the outgrowth of axon-like processes in N2a cells after a 24-h exposure but neither compound affected process outgrowth by differentiating C6 cells at these concentrations. Under these conditions, 10 microM diazinon inhibited AChE slightly compared to the control after a 4-h exposure but not after 24 h. Western blotting analysis showed that morphological changes were associated with reduced cross-reactivity with antibodies that recognize the neurofilament heavy chain (NFH), microtubule associated protein MAP 1B and HSP-70 compared to control cell extracts, whereas reactivity with anti-alpha-tubulin antibodies was unchanged. Aggregation of NFH was observed in cell bodies of diazinon-treated N2a cells, as determined by indirect immunofluorescence staining. These data demonstrate that diazinon specifically targets neurite outgrowth in neuronal cells and that this effect is associated with disruption of axonal cytoskeleton proteins, whereas cypermethrin has no effect on the same parameters.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2011","Flaskos, J., Nikolaidis, E., Harris, W., Sachana, M., Hargreaves, A. J.","Effects of sub-lethal neurite outgrowth inhibitory concentrations of chlorpyrifos oxon on cytoskeletal proteins and acetylcholinesterase in differentiating N2a cells","Toxicology and applied pharmacology","256(3):330-6","a3679571-dcfd-42c1-b593-f467e00500de","","Previous work in our laboratory has shown that sub-lethal concentrations (1-10 muM) of chlorpyrifos (CPF), diazinon (DZ) and diazinon oxon (DZO) inhibit the outgrowth of axon-like neurites in differentiating mouse N2a neuroblastoma cells concomitant with altered

levels and/or phosphorylation state of axonal cytoskeleton and growth-associated proteins. The aim of the present work was to determine whether chlorpyrifos oxon (CPO) was capable of inhibiting N2a cell differentiation in a similar manner. Using experimental conditions similar to our previous work, sub-lethal concentrations (1-10 muM) of CPO were found to inhibit N2a cell differentiation. However, unlike previous studies with DZ and DZO, there was a high level of sustained inhibition of acetylcholinesterase (AChE) in CPO treated cells. Impairment of neurite outgrowth was also associated with reduced levels of growth associated protein-43 and neurofilament heavy chain (NFH), and the distribution of NFH in cells stained by indirect immunofluorescence was disrupted. However, in contrast to previous findings for DZO, the absolute level of phosphorylated NFH was unaffected by CPO exposure. Taken together, the findings suggest that sub-lethal concentrations of CPO inhibit axon outgrowth in differentiating N2a cells and that this effect involves reduced levels of two proteins that play key roles in axon outgrowth and maintenance. Although the inhibition of neurite outgrowth is unlikely to involve AChE inhibition directly, further work will help to determine whether the persistent inhibition of AChE by CPO can account for the different effects induced by CPO and DZO on the levels of total and phosphorylated NFH.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Harris, W., Sachana, M., Flaskos, J., Hargreaves, A. J.","Proteomic analysis of differentiating neuroblastoma cells treated with sub-lethal neurite inhibitory concentrations of diazinon: identification of novel biomarkers of effect","Toxicology and applied pharmacology","240(2):159-65","1493a492-82f6-4e18-a85f-8c65ce6250f3","","In previous work we showed that sub-lethal levels of diazinon inhibited neurite outgrowth in differentiating N2a neuroblastoma cells. Western blotting analysis targeted at proteins involved in axon growth and stress responses, revealed that such exposure led to a reduction in the levels of neurofilament heavy chain, microtubule associated protein 1 B (MAP 1B) and HSP-70. The aim of this study was to apply the approach of 2 dimensional polyacrylamide gel electrophoresis and mass spectrometry to identify novel biomarkers of effect. A number of proteins were found to be up-regulated compared to the control on silver-stained gels. These were classified in to 3 main groups of proteins: cytosolic factors, chaperones and the actin-binding protein cofilin, all of which are involved in cell differentiation, survival or metabolism. The changes observed for cofilin were further confirmed by quantitative Western blotting analysis with anti-actin and anti-cofilin antibodies. Indirect immunofluorescence staining with the same antibodies indicated that the microfilament network was disrupted in diazinon-treated cells. Our data suggest that microfilament organisation is disrupted by diazinon exposure, which may be related to increased cofilin expression.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Pina-Guzman, B., Solis-Heredia, M. J., Quintanilla-Vega, B.","Diazinon alters sperm chromatin structure in mice by phosphorylating nuclear protamines","Toxicology and applied pharmacology","202(2):189-98","b06a3308-c76b-44d0-97e6-b5accce32273","","Organophosphorus (OP) pesticides, widely used in agriculture and pest control, are associated with male reproductive effects, including sperm chromatin alterations, but the mechanisms underlying these effects are unknown. The main toxic action of OP is related to phosphorylation of proteins. Chemical alterations in sperm nuclear proteins (protamines), which pack DNA during the last steps of spermatogenesis, contribute to male reproductive toxicity. Therefore, in the present study, we tested the ability of diazinon (DZN), an OP compound, to alter

sperm chromatin by phosphorylating nuclear protamines. Mice were injected with a single dose of DZN (8.12 mg/kg, i.p.), and killed 8 and 15 days after treatment. Quality of sperm from epididymis and vas deferens was evaluated through standard methods and chromatin condensation by flow cytometry (DNA Fragmented Index parameters: DFI and DFI%) and fluorescence microscopy using chromomycin-A(3) (CMA(3)). Increases in DFI (15%), DFI% (4.5-fold), and CMA(3) (2-fold) were observed only at 8 days post-treatment, indicating an alteration in sperm chromatin condensation and DNA damage during late spermatid differentiation. In addition, an increase of phosphorous content (approximately 50%) in protamines, especially in the phosphoserine content (approximately 73%), was found at 8 days post-treatment. Sperm viability, motility, and morphology showed significant alterations at this time. These data strongly suggest that spermatozoa exposed during the late steps of maturation were the targets of DZN exposure. The correlation observed between the phosphorous content in nuclear protamines with DFI%, DFI, and CMA(3) provides evidence that phosphorylation of nuclear protamines is involved in the OP effects on sperm chromatin.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Slotkin, T. A., Seidler, F. J.","Developmental neurotoxicants target neurodifferentiation into the serotonin phenotype: Chlorpyrifos, diazinon, dieldrin and divalent nickel","Toxicology and applied pharmacology","233(2):211-9","28450b55-4daa-4bc5-b814-57125112f9e0","","Developmental exposure to organophosphates (OP) produces long-term changes in serotonin (5HT) synaptic function and associated behaviors, but there are disparities among the different OPs. We contrasted effects of chlorpyrifos and diazinon, as well as non-OP neurotoxicants (dieldrin, Ni(2+)) using undifferentiated and differentiating PC12 cells, a well-established neurodevelopmental model. Agents were introduced at 30 microM for 24 or 72 h, treatments devoid of cytotoxicity, and we evaluated the mRNAs encoding the proteins for 5HT biosynthesis, storage and degradation, as well as 5HT receptors. Chlorpyrifos and diazinon both induced tryptophan hydroxylase, the rate-limiting enzyme for 5HT biosynthesis, but chlorpyrifos had a greater effect, and both agents suppressed expression of 5HT transporter genes, effects that would tend to augment extracellular 5HT. However, whereas chlorpyrifos enhanced the expression of most 5HT receptor subtypes, diazinon evoked overall suppression. Dieldrin evoked even stronger induction of tryptophan hydroxylase, and displayed a pattern of receptor effects similar to that of diazinon, even though they come from different pesticide classes. In contrast, Ni(2+) had completely distinct actions, suppressing tryptophan hydroxylase and enhancing the vesicular monoamine transporter, while also reducing 5HT receptor gene expression, effects that would tend to lower net 5HT function. Our findings provide some of the first evidence connecting the direct, initial mechanisms of developmental neurotoxicant action on specific transmitter pathways with their long-term effects on synaptic function and behavior, while also providing support for in vitro test systems as tools for establishing mechanisms and outcomes of related and unrelated neurotoxicants.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Mehrani, H., Golmanesh, L.","Changes in mRNA and protein levels of nicotinic acetylcholine receptors in Diazoxon exposed pC12 cells","Toxicology in vitro : an international journal published in association with BIBRA","22(5):1257-63","01cb14a1-3fb5-44ce-99ee-1c00dde7f6c5","","Effects of diazoxon on the gene and protein expression of nicotinic

acetylcholine receptors (nAChR) were evaluated in PC12 cells. Cells were exposed to 100 microM diazoxon for 48 h in the presence versus absence of nAChR agonists or antagonists. Diazoxon significantly inhibited AChE activity in the cells. At the mRNA level, transcripts of the alpha4 and beta2 subunits of nAChR were significantly reduced in cells exposed to diazoxon, but there was no change in alpha7 subunit mRNA content. Diazoxon exposure also significantly reduced the protein levels of both alpha4 and beta2 nAChR subunits. Treatment with nicotine (10 microM) or with the nicotinic receptor antagonists, mecamylamine (10 microM) or dihydro-beta-erythroidine (DHbetaE) (5 microM) efficiently prevented the diazoxon-induced reduction in alpha4 and beta2 nAChR mRNA and protein in PC12 cells, but carbamaylcholine, a weak nAChR agonist, was ineffective. These data suggest that alpha4beta2 nAChRs are involved in diazoxon-related toxicity and that nicotinic receptor antagonists could play a protective role against organophosphate-related damage.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Sidiropoulou, E., Sachana, M., Flaskos, J., Harris, W., Hargreaves, A. J., Woldehiwet, Z.","Diazinon oxon interferes with differentiation of rat C6 glioma cells","Toxicology in vitro : an international journal published in association with BIBRA","23(8):1548-52","029d13ea-a259-45ad-8338-f2ba5a067cb5","","The purpose of this study was to evaluate the toxicity of diazinon oxon (DZO), a major in vivo metabolite of the organophosphate insecticide diazinon (DZ), on differentiating rat C6 glioma cells. At concentrations shown to be non-cytotoxic by both the MTT and the Kenacid blue dye binding assays (1, 5 and 10 microM), DZO caused after 24h a reduction in the number of extensions developed from C6 cells induced to differentiate by serum withdrawal and addition of sodium butyrate. Densitometric scanning of Western blots of extracts of C6 cells demonstrated that, at all concentrations used, DZO decreased after 24h the expression of glial fibrillary acidic protein (GFAP) compared to controls. In addition, exposure to 10 microM DZO for 24h reduced the levels of tubulin and microtubule associated protein 1B (MAP1B). On the other hand, levels of MAP2c were not affected by DZO treatment. In contrast to our previous data on DZ, the above findings suggest that its oxon metabolite, DZO, may, at biologically relevant, subcytotoxic concentrations, interfere with glial cell differentiation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Lari, P., Abnous, K., Imenshahidi, M., Rashedinia, M., Razavi, M., Hosseinzadeh, H.","Evaluation of diazinon-induced hepatotoxicity and protective effects of crocin","Toxicology and industrial health","31(4):367-76","9a013479-24e7-4ee9-8b60-090fcb6b032e","","Diazinon (DZN) is one of the most widely used insecticides in agricultural pest control. Previous studies have shown that DZN may induce hepatotoxicity. Reactive oxygen species and apoptosis pathways are involved in the toxicity of DZN. Crocin, a constituent of saffron, has hepatoprotective effects due to its antioxidant activity. In this study, we examined the effects of subacute DZN exposure and ameliorating effect of crocin on lipid peroxidation and pathological changes in rat liver. Moreover, protein levels of activated and total caspases-3 and -9 and Bax/Bcl-2 ratio were measured. Five groups of rats were used in the experiment. Corn oil (control), DZN (15 mg/kg per day, orally) and crocin (12.5, 25 and 50 mg/kg per day, intraperitoneally in combination with DZN) were given to male Wistar rats (n = 6) for 4 weeks. The level of malondialdehyde (MDA) increased significantly in DZN group compared with the control group ($p < 0.05$). MDA level decreased significantly in the group that received DZN plus 25 mg crocin ($p < 0.001$). No gross or histological evidence of treatment-related damage to the liver

after oral exposure to DZN was observed. DZN also induced apoptosis through activation of caspases-9 and -3 and increasing Bax/Bcl-2 ratio. Crocin attenuated the activation of caspases and reduced the Bax/Bcl-2 ratio. It is concluded that subacute exposure to DZN induces oxidative stress-mediated apoptosis and crocin may reduce DZN-induced hepatotoxicity.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Messarah, M., Amamra, W., Boumendjel, A., Barkat, L., Bouasla, I., Abdennour, C., Boulakoud, M. S., Feki, A. E.","Ameliorating effects of curcumin and vitamin E on diazinon-induced oxidative damage in rat liver and erythrocytes","Toxicology and industrial health","29(1):77-88","6457c01b-f8c3-431e-b357-7e391b766ded","","The aim of this study was to evaluate the protective effects of vitamin E and/or curcumin against diazinon (DZN) (an organophosphorus insecticide)-induced toxicity of blood, liver and erythrocyte markers of male Wistar rats. The exposure of rats to DZN for 21 days provoked significant changes in red blood cell counts and hemoglobin. Results showed that lipid peroxidation increased significantly in DZN-treated rats, as evidenced by high liver and erythrocyte thiobarbituric acid reactive substance levels. Alteration of the antioxidant system in DZN-treated rats was confirmed by the significant decrease in the activity of catalase, glutathione peroxidase and glutathione-S-transferase, accompanied by a decline in reduced glutathione content in both tissues. On the other hand, a significant increase in the activities of plasma aspartate transaminase, alanine transaminase, lactate dehydrogenase and alkaline phosphatase was observed in the rats treated with DZN. However, the administration of vitamin E and curcumin has ameliorated the previous markers. In conclusion, our results indicate that the natural antioxidants like vitamin E and curcumin can effectively lower the erythrocytes and hepatic injuries induced by DZN as monitored by lipid peroxides, antioxidant enzyme activities and sensitive serum enzyme levels.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Moallem, S. A., Hariri, A. T., Mahmoudi, M., Hosseinzadeh, H.","Effect of aqueous extract of Crocus sativus L. (saffron) stigma against subacute effect of diazinon on specific biomarkers in rats","Toxicology and industrial health","30(2):141-6","bf8016fa-9e9e-4162-af0f-f8ac62218bc7","","In this study, the effect of aqueous extract of Crocus sativus L. (saffron) stigma was studied against subacute toxicity of diazinon (DZN) on specific biochemical markers in rats. Vitamin E (200 IU/kg) and the aqueous extract of saffron at doses 50, 100 and 200 mg/kg were injected intraperitoneally three times per week alone or with DZN (20 mg/kg/day, orally) for 4 weeks. Red blood cell (RBC) cholinesterase activity was inhibited by DZN and this effect was not affected by vitamin E or saffron plus DZN. The levels of serum tumor necrosis factor-alpha (inflammation marker), direct 8-iso-prostaglandin F(2alpha) (oxidative stress marker) and soluble protein-100 beta (S100beta, neuronal damage marker) were increased significantly by DZN. The saffron extract inhibited the effect of DZN on these biomarkers levels. However, vitamin E was able to only reduce 8-iso-prostaglandin F(2alpha) and S100beta levels. This study showed that the aqueous extract of saffron prevents DZN-induced rise of several specific inflammation, oxidative stress and neuronal damage biomarkers.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2000","Cha, S. W., Gu, H. K., Lee, K. P., Lee, M. H., Han, S. S., Jeong, T. C.","Immunotoxicity of ethyl carbamate in female BALB/c mice: role of esterase and cytochrome P450","Toxicology letters","115(3):173-81","3e5fbfa0-4b83-4450-8293-c2e5f3b3f724","","Ethyl carbamate, a potent carcinogen,

has been characterized to be metabolized by cytochrome P450 (P450) and esterase. It has recently been demonstrated that P450 may activate ethyl carbamate to immunotoxic metabolites. To investigate the role of esterase in ethyl carbamate-induced immunosuppression, mice were pretreated intraperitoneally with an esterase inhibitor, diazinon, at 20 mg/kg 30 min prior to the administration of ethyl carbamate intraperitoneally at 100 and 400 mg/kg for 7 consecutive days. Pretreatment with diazinon completely blocked the serum esterase activity. Histopathologically splenic and thymic atrophy was observed when mice were treated with ethyl carbamate, which was potentiated by the pretreatment with diazinon. In spleen, lymphocytes in the periarteriolar lymphoid sheath and the marginal zone appeared to be depleted in the white pulps. In thymus, ethyl carbamate caused a marked depletion of cells in cortex. The antibody response to sheep red blood cells (SRBCs) was more suppressed by ethyl carbamate in diazinon-pretreated groups than in corn oil-pretreated groups. These results suggest that the metabolism of ethyl carbamate by esterase may be an inactivation pathway in ethyl carbamate-induced immunosuppression. In addition, ethyl N-hydroxycarbamate, a P450 metabolite, suppressed the lymphoproliferative response induced by lipopolysaccharide and concanavalin A in splenocyte cultures. These results indicate that the metabolism of ethyl carbamate by P450 may be an activation pathway in immunosuppression by ethyl carbamate.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Lecoeur, S., Videmann, B., Mazallon, M.","Effect of organophosphate pesticide diazinon on expression and activity of intestinal P-glycoprotein","Toxicology letters","161(3):200-9","653513fc-810f-490b-96f6-5401645c6c46","","Organophosphate insecticide diazinon is widely used in agricultural practices, submitting farmers to repeated exposure. Because efflux pumps, as P-glycoprotein (P-gp), serve both as natural defense mechanisms and influence the bioavailability and disposition of drugs, we analyzed the ability of diazinon to act as efflux modulator. Oral administration of diazinon (2-20 mg/kg, 5 days, or 10 mg/kg, 2-12 days) increased intestinal mdr1a mRNA of rats, in both dose- and time-dependent manner, and increased the expression of intestinal P-gp. Using the intestinal cell-line Caco-2, we found that 100 microM diazinon significantly inhibited digoxin and vinblastine secretive flux through the cell monolayers, whereas digoxin and vinblastine absorptive flux increased. The 25 microM diazinon was transported preferentially in basolateral (BL) to apical (AP) direction, suggesting a net secretion. The efflux rate significantly decreased in the presence of metabolic inhibitors sodium azide and 2-deoxy-d-glucose, P-gp inhibitors cyclosporin A and valspodar, but not in the presence of MRPs inhibitor MK571. Repeated exposure of Caco-2 cells to diazinon increased P-glycoprotein expression and activity. These results suggested the involvement of P-gp in the transfer of diazinon, leading to potential consequences for xenobiotic interactions, and showed that repeated exposure to low doses of pesticide may lead to up-regulated P-gp functions in the intestine of
mammals.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Peeples, E. S., Schopfer, L. M., Duysen, E. G., Spaulding, R., Voelker, T., Thompson, C. M., Lockridge, O.","Albumin, a new biomarker of organophosphorus toxicant exposure, identified by mass spectrometry","Toxicological sciences : an official journal of the Society of Toxicology","83(2):303-12","f23c5f45-705d-4c51-bcf6-6e6174b48aac","","The classical laboratory tests for exposure to organophosphorus toxicants (OP) are inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity in blood. In a

search for new biomarkers of OP exposure, we treated mice with a biotinylated organophosphorus agent, FP-biotin. The biotinylated proteins in muscle were purified by binding to avidin-Sepharose, separated by gel electrophoresis, digested with trypsin, and identified from their fragmentation patterns on a quadrupole time-of-flight mass spectrometer. Albumin and ES1 carboxylesterase (EC 3.1.1.1) were found to be major targets of FP-biotin. These FP-biotinylated proteins were also identified in mouse plasma by comparing band patterns on nondenaturing gels stained for albumin and carboxylesterase activity, with band patterns on blots hybridized with Streptavidin Alexa-680. Two additional FP-biotin targets, AChE (EC 3.1.1.7) and BChE (EC 3.1.1.8), were identified in mouse plasma by finding that enzyme activity was inhibited 50-80%. Mouse plasma contained eight additional FP-biotinylated bands whose identity has not yet been determined. In vitro experiments with human plasma showed that chlorpyrifos oxon, echothiophate, malaoxon, paraoxon, methyl paraoxon, diazoxon, diisopropylfluorophosphate, and dichlorvos competed with FP-biotin for binding to human albumin. Though experiments with purified albumin have previously shown that albumin covalently binds OP, this is the first report of OP binding to albumin in a living animal. Carboxylesterase is not a biomarker in man because humans have no carboxylesterase in blood. It is concluded that OP bound to albumin could serve as a new biomarker of OP exposure in man.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Shao, J., Katika, M. R., Schmeits, P. C., Hendriksen, P. J., van Loveren, H., Peijnenburg, A. A., Volger, O. L.","Toxicogenomics-based identification of mechanisms for direct immunotoxicity","Toxicological sciences : an official journal of the Society of Toxicology","135(2):328-46","2f86f330-a603-4d68-a65d-3f005eb0b259","","Compounds with direct immunotoxic properties, including metals, mycotoxins, agricultural pesticides, and industrial chemicals, form potential human health risks due to exposure through food, drinking water, and the environment. Insights into the mechanisms of action are currently lacking for the majority of these direct immunotoxicants. Therefore, the present work aimed to gain insights into the molecular mechanisms underlying direct immunotoxicity. To this end, we assessed in vitro the effects of 31 test compounds on the transcriptome of the human Jurkat T-cell line. These compounds included direct immunotoxicants, immunosuppressive drugs with different mode of actions, and nonimmunotoxic control chemicals. Pathway analysis of the microarray data allowed us to identify canonical pathways and Gene Ontology processes that were transcriptionally regulated in common by immunotoxicants (1) with structural similarities, such as tributyltin chloride and tributyltin oxide that activated the retinoic acid/X receptor signaling pathway and (2) without structural similarities, such as As2O3, dibutyltin chloride, diazinon, MeHg, ochratoxin A (OTA), S9-treated OTA, S9-treated cyclophosphamide, and S9-treated benzo[a]pyrene, which activated unfolded protein response, and FTY720, lindane, and propanil, which activated the cholesterol biosynthesis pathway. In addition, processes uniquely affected by individual immunotoxicants were identified, such as the induction of Notch receptor signaling and the downregulation of acute-phase response genes by OTA. These findings were validated by quantitative real-time PCR analysis of genes involved in these processes. Our study indicated that diverse modes of action are involved in direct immunotoxicity and that a set of pathways or genes, rather than one single gene, can be used to screen compounds for direct immunotoxicity.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Thomas, R. S., Pluta, L., Yang,

L., Halsey, T. A.","Application of genomic biomarkers to predict increased lung tumor incidence in 2-year rodent cancer bioassays","","97(1):55-64","ba37f702-4255-49b3-ad95-9f7743bb22b6","","Rodent cancer bioassays are part of a legacy of safety testing that has not changed significantly over the past 30 years. The bioassays are expensive, time consuming, and use hundreds of animals. Fewer than 1500 chemicals have been tested in a rodent cancer bioassay compared to the thousands of environmental and industrial chemicals that remain untested for carcinogenic activity. In this study, we used existing data generated by the National Toxicology Program (NTP) to identify gene expression biomarkers that can predict results from a rodent cancer bioassay. A set of 13 diverse chemicals was selected from those tested by the NTP. Seven chemicals were positive for increased lung tumor incidence in female B6C3F1 mice and six were negative. Female mice were exposed subchronically to each of the 13 chemicals, and microarray analysis was performed on the lung. Statistical classification analysis using the gene expression profiles identified a set of eight probe sets corresponding to six genes whose expression correctly predicted the increase in lung tumor incidence with 93.9% accuracy. The sensitivity and specificity were 95.2 and 91.8%, respectively. Among the six genes in the predictive signature, most were enzymes involved in endogenous and xenobiotic metabolism, and one gene was a growth factor receptor involved in lung development. The results demonstrate that increases in chemically induced lung tumor incidence in female mice can be predicted using gene biomarkers from a subchronic exposure and may form the basis of a more efficient and economical approach for evaluating the carcinogenic activity of chemicals. Â© The Author 2007. Published by Oxford University Press on behalf of the Society of Toxicology. All rights reserved.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2002","Axelrad, J. C., Howard, C. V., McLean, W. G.","Interactions between pesticides and components of pesticide formulations in an in vitro neurotoxicity test","Toxicology","173(3):259-68","96381604-c6ad-451e-a544-10c28b901faf","","Organophosphate (OP) pesticides are often used in combination with one another and with the components of formulations. Evidence already exists for interactions in the neurotoxic effects of OPs through interference with metabolism, but there is also potential for interactions related directly to cell damage. The purpose of this work was to investigate this possibility for OPs and the components of one of their common formulations in vitro. NB2a neuroblastoma cells were induced to differentiate in the presence of the OPs diazinon and chlorpyrifos, in combination with a commercial formulation (identified as Commercial Formulation 1) of the compounds and, independently, the components of that formulation. The compounds were tested in pairs in various proportions and the resulting inhibition of neurite outgrowth was measured by light microscopy and quantitative image analysis. Interactions were determined in terms of enhanced or reduced effects of the paired compounds in comparison with the expected additive effects estimated from the effects of each compound on its own. Synergism was detected between combinations of: 10 microM chlorpyrifos and 500 nM pyrethrum; chlorpyrifos and one of the solvents (regular spirit) found in Commercial Formulation 1. All other combinations of OPs and products were additive in their neurotoxicity. The data suggest that exposure to multiple OP-containing pesticide formulations may lead to synergistic neurotoxicity by a direct mechanism at the cellular level.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2003","Axelrad, J. C., Howard, C. V., McLean, W. G.","The effects of acute pesticide exposure on neuroblastoma cells

chronically exposed to diazinon","Toxicology","185(1-2):67-78","57a8a2e5-adf2-4fcc-91cf-ddb6ed069d09","","Speculation about potential neurotoxicity due to chronic exposure to low doses of organophosphate (OP) pesticides is not yet supported by experimental evidence. The objective of this work was to use a cell culture model of chronic OP exposure to determine if such exposure can alter the sensitivity of nerve cells to subsequent acute exposure to OPs or other compounds. NB2a neuroblastoma cells were grown in the presence of 25 microM diazinon for 8 weeks. The OP was then withdrawn and the cells were induced to differentiate in the presence of various other pesticides or herbicides, including OPs and OP-containing formulations. The resulting outgrowth of neurite-like structures was measured by light microscopy and quantitative image analysis and the IC(50) for each OP or formulation was calculated. The IC(50) values in diazinon-pre-exposed cells were compared with the equivalent values in cells not pre-exposed to diazinon. The IC(50) for inhibition of neurite outgrowth by acute application of diazinon, pyrethrum, glyphosate or a commercial formulation of glyphosate was decreased by between 20 and 90% after pre-treatment with diazinon. In contrast, the IC(50) for pirimiphos methyl was unaffected and those for phosmet or chlorpyrifos were increased by between 1.5- and 3-fold. Treatment of cells with chlorpyrifos or with a second glyphosate-containing formulation led to the formation of abnormal neurite-like structures in diazinon-pre-exposed cells. The data support the view that chronic exposure to an OP may reduce the threshold for toxicity of some, but by no means all, environmental agents.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2005","Guizzetti, M., Pathak, S., Giordano, G., Costa, L. G.","Effect of organophosphorus insecticides and their metabolites on astroglial cell proliferation","Toxicology","215(3):182-90","7e54409a-878b-4900-82e2-961217857f16","","Though little attention has been given to the possibility that glial cells may represent a target for the developmental neurotoxicity of organophosphorus (OP) insecticides, recent evidence, obtained in particular with chlorpyrifos (CP), suggests that developmental exposure to this compound may indeed target astrocytes. To substantiate and expand these observations, we carried out a series of in vitro studies utilizing fetal rat astrocytes and a human astrocytoma cell line, 1321N1 cells, to investigate the effect of the OPs CP, diazinon (DZ) and parathion (P), their oxygen analogs chlorpyrifos oxon (CPO), diazoxon (DZO) and paraoxon (PO), and their metabolites 3,5,6-trichloro-2-pyridinol (TCP), 2-isopropyl-6-methyl-4-pyrimidol (IMP) and para-nitrophenol (PNP), on cell proliferation. In fetal rat astrocytes and astrocytoma cells maintained in serum, CP, DZ, P, CPO, DZO, and PO induced a concentration-dependent inhibition in [(3)H]thymidine incorporation with a very similar potency (IC(50) between 45 and 57 microM). Among the other metabolites, PNP was the most potent (IC(50)=70-80 microM), while TCP and IMP were much less effective (IC(50)>100 microM). Cytotoxicity appears to account only for a small part of the effect on DNA synthesis. OP insecticides and their oxons were three- to six-fold more potent in inhibiting [(3)H]thymidine incorporation when cells were synchronized in the G(0)/G(1) phase of the cell cycle and re-stimulated by carbachol or epidermal growth factor. These results suggest that OP insecticides and their oxons affect astroglial cell proliferation and that the transition from the G(0)/G(1) to the S/G(2) phase of the cell cycle may be particularly sensitive to the action of these compounds.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2014","Lasram, M. M., Dhouib, I. B., Annabi, A., El Fazaa, S., Gharbi, N.","A review on the molecular mechanisms involved in

insulin resistance induced by organophosphorus pesticides","","322:1-13","fd7b2d4f-53f4-4950-88e2-f8e3a9478e05","","There is increasing evidence reporting that organophosphorus pesticides (OPs) impair glucose homeostasis and cause insulin resistance and type 2 diabetes. Insulin resistance is a complex metabolic disorder that defies explanation by a single etiological pathway. Formation of advanced glycation end products, accumulation of lipid metabolites, activation of inflammatory pathways and oxidative stress have all been implicated in the pathogenesis of insulin resistance. Ultimately, these molecular processes activate a series of stress pathways involving a family of serine kinases, which in turn have a negative effect on insulin signaling. Experimental and clinical data suggest an association between these molecular mechanisms and OPs compounds. It was first reported that OPs induce hyperglycemia. Then a concomitant increase of blood glucose and insulin was pointed out. For some years only, we have begun to understand that OPs promote insulin resistance and increase the risk of type 2 diabetes. Overall, this review outlines various mechanisms that lead to the development of insulin resistance by OPs exposure. Â© 2014 Elsevier Ireland Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1996","Marinovich, M., Ghilardi, F., Galli, C. L.","Effect of pesticide mixtures on in vitro nervous cells: comparison with single pesticides","Toxicology","108(3):201-6","eb007791-031f-447d-b698-bd0fe5dbda79","","The toxicity of dimethoate, azinphos-methyl, diazinon, pirimiphos methyl, organophosphorus insecticides, and benomyl (a benzimidazole fungicide) singly and in mixture was studied in a human neuroblastoma cell line, SH-SY5Y. The cells were incubated for 30 min and 4 h with pesticides at concentrations ranging from 0.4 to 100 micrograms/ml, or with the same compounds mixed as follows: (a) dimethoate-diazinon-azinphos; (b) benomyl-pirimiphos; (c) all together. Pesticides in the mixtures were at the same concentration used when tested singly. Diazinon, azinphos-methyl and pirimiphos, but not dimethoate and benomyl, inhibited acetylcholine esterase (AchE) activity, whereas all the compounds inhibited protein synthesis in the following order: benomyl > azinphos > diazinon >> pirimiphos = dimethoate. The mixtures showed a toxicity on AchE activity at a maximum equal to that of the most active compound in the mixture. On the contrary, the mixture were more toxic than the single compounds on protein synthesis, and in certain cases potentiation occurred. Therefore, we can conclude that it is not feasible to predict the toxicity of pesticide mixtures on the basis of the results of the toxicity of single components.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Merhi, M., Demur, C., Racaud-Sultan, C., Bertrand, J., Canlet, C., Estrada, F. B. Y., Gamet-Payrastre, L.","Gender-linked haematopoietic and metabolic disturbances induced by a pesticide mixture administered at low dose to mice","","267(1-3):80-90","bf9529c9-092c-4074-862d-6d6f40534dd2","","Defining the impact on health of exposure to a low-dose pesticide mixture via food intake is a topical question since epidemiological studies suggest that this may increase the risk of pathologies and particularly haematopoietic malignancies. Here we investigated on the haematopoietic system of mice, the effect of a mixture of six pesticides frequently ingested through the intake of fruits and vegetables produced in France (alachlor, captan, diazinon, endosulfan, maneb, mancozeb). The mixture was administered repeatedly by gavage to mice for 4 weeks at levels derived from the human Acceptable Daily Intake (ADI) level adapted to the mean weight of mice. Using a NMR-based metabonomic approach, we show that this treatment led

to specific gender-linked variations in the level of hepatic metabolites involved in oxidative stress and in the regulation of glucose metabolism, indicating a metabolic signature for this repeated administration. Interestingly, exposure to the low-dose pesticide mixture induced significant changes in the blood cell counts with modifications in the clonogenic and differentiating capacities of haematopoietic progenitors showing abnormalities in the granulocytic and monocytic lineages in female and male mice, respectively. From a molecular point of view, the changes induced by the pesticide treatment correlated with modifications of the PI 3-kinase/Akt signalling pathway, the tyrosine kinase Pyk2 and the c-Myc transcription factor, which are involved in the balance between self-renewal and differentiation of haematopoietic stem cells. Our results point to a significant effect of a very low dose of a mixture of commonly used pesticides on mice metabolism and haematopoietic system with major differences between males and females. Â© 2009 Elsevier Ireland Ltd. All rights reserved.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Mostafalou, S., Abdollahi, M.","Pesticides and human chronic diseases: Evidences, mechanisms, and perspectives","","268(2):157-177","a1cbbf6c-7d13-45f3-8cf2-9a43f95098dd","","Along with the wide use of pesticides in the world, the concerns over their health impacts are rapidly growing. There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as different types of cancers, diabetes, neurodegenerative disorders like Parkinson, Alzheimer, and amyotrophic lateral sclerosis (ALS), birth defects, and reproductive disorders. There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD), cardiovascular disease such as atherosclerosis and coronary artery disease, chronic nephropathies, autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis, chronic fatigue syndrome, and aging. The common feature of chronic disorders is a disturbance in cellular homeostasis, which can be induced via pesticides' primary action like perturbation of ion channels, enzymes, receptors, etc., or can as well be mediated via pathways other than the main mechanism. In this review, we present the highlighted evidence on the association of pesticide's exposure with the incidence of chronic diseases and introduce genetic damages, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress and unfolded protein response (UPR), impairment of ubiquitin proteasome system, and defective autophagy as the effective mechanisms of action. Â© 2013 Elsevier Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Ahmadi, K., Mirvaghefei, A. R., Banaee, M., Vosoghei, A. R.","Effects of long-term diazinon exposure on some immunological and haematological parameters in rainbow trout Oncorhynchus mykiss (Walbaum, 1792)","","6(1):1-7","c94f57f3-0681-479b-ad97-253482c699e7","","Metagenome analysis was used to monitor changes in microbial population during the industrial-scale batch fermentation period (0, 15 days and 2 years). Genomic DNA was extracted from Bachu-Kimchi samples and was sequenced using GS Junior Titanium system, which yielded a total 6886, 6271, and 6621 reads from 0, 15 days and 2 years samples, respectively. Phylogenetic analysis based on 16S rRNA sequences showed clearly that microbial population was changed depending on the fermentation process (initial, rancid, and over-ripening stage). Wessella sp. and Leuconostoc sp. became the predominant group in microbial community at the optimumrancid stage (15 days), but as

the fermentation progressed more, the abundance of Lactobacillus sp. and Bacillus sp. increased (2 years). Moreover, the specific kimchi microbes in the industrial-scale fermentation process were isolated: Leuconostoc mesenteroides, Lactobacillus sakei, Lactobacillus plantarum, and Weissella koreensis. Â© 2014 Korean Society of Environmental Risk Assessment and Health Science and Springer Science+Business Media Dordrecht.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Wierucka, M., Biziuk, M.","Application of magnetic nanoparticles for magnetic solid-phase extraction in preparing biological, environmental and food samples","","59:50-58","0e19fae3-7897-4834-a893-de83bdcbbad5","","The need to obtain meaningful results as the basis for determining the content of trace amounts of analytes has become the driving force behind the development of modern analytical techniques, including sample-preparation techniques, such as solid-phase extraction (SPE). Recently, great interest was aroused in the use of magnetic nanoparticles (MNPs) in SPE. These materials exhibit high selectivity, and, in small amounts, can provide high recovery of analytes, even from large-volume samples. MNPs allow easy, rapid isolation of analytes using an external magnetic field. Simplicity in use, ease of surface modification and the versatility of MNPs mean that they are now widely used in many fields, including biotechnology, medicine and analytical chemistry. In magnetic SPE, these materials provide effective isolation and/or enrichment of the analytes, from samples with complex matrices (e.g. biological, environmental and food samples). Â© 2014 Elsevier B.V.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Guest, R. K., Ikehata, K., El-Din, M. G., Smith, D. W.","Pesticides and herbicides","","78(10):1755-1801","24d20845-7a19-4ab0-8e0d-5992b460bb66","","","","","RefMan","","","","","","","","","","